FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

AND THE

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

8:10 a.m.

Wednesday, December 13, 1995

Plaza Ballroom
Holiday Inn
8777 Georgia Avenue

Silver Spring, Maryland

APPEARANCES

ANTI-INFECTIVE DRUGS ADVISORY
COMMITTEE MEMBERS PRESENT:

WILLIAM A. CRAIG, M.D., Chairman
Chief, Infectious Diseases
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Clinical Pharmacology Research Center
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CARL W. NORDEN, M.D.
Head, Division of Infectious Diseases
Cooper Hospital/University Medical Center
Department of Medicine
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APPEARANCES (Continued)

ANTI-INFECTIVE DRUGS ADVISORY
COMMITTEE MEMBERS PRESENT: (Continued)

ROSELYN J. RICE, M.D.
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Division of Sexually Transmitted
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GASTROINTESTINAL DRUGS ADVISORY
COMMITTEE MEMBERS PRESENT:

ROSEMARIE FISHER, M.D., Chairman
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JAMES BUTT II, M.D.
Harry S. Truman Memorial Veterans
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GAIL COMER, M.D.
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APPEARANCES (Continued)

GASTROINTESTINAL DRUGS ADVISORY
COMMITTEE MEMBERS PRESENT: (Continued)

JANET ELASHOFF, Ph.D.
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BARBARA KIRSCHNER, M.D.
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VOTING COMMITTEE CONSULTANTS PRESENT:

J. KAY DUNN, Ph.D.
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FRANKLYN JUDSON, M.D.
Professor, Departments of Medicine
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BARTH RELLER, M.D.
Director of Clinical Microbiology
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APPEARANCES (Continued)

NON-VOTING COMMITTEE CONSULTANTS PRESENT:

LOREN LAINE, M.D.
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Department of Medicine
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KENNETH R. McQUAID, M.D.
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Assistant chief, Gastroenterology
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PROFESSOR FRANCIS MEGRAUD
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JOHN H. WALSH, M.D.
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and Education
Gastroenteric Biology Center
West Los Angeles VA Medical Center
Los Angeles, California 90073-1792

FOOD AND DRUG ADMINISTRATION STAFF PRESENT:

PAUL BOTSTEIN, M.D.
MARY FANNING, M.D.
DAVID FEIGAL, M.D.
STEPHEN FREDD, M.D.
LUIGI GIRARDI, M.D.
ROBERT HOPKINS, M.D.
NASIM MOLEDINA, M.D.
ROBERT PRIZONT, M.D.
ROBERT TEMPLE, M.D.
ELIZABETH TURNEY, M.S.
LINDA UTRUP, Ph.D.

APPEARANCES (Continued)

ABBOTT LABORATORIES REPRESENTATIVES PRESENT:

CARL CRAFT, M.D.
RICHART HUNT, M.D.
ANDRE PERNET, Ph.D.
DAVID PIZZUTI, M.D.
NANCY SIEPMAN, Ph.D.
KEN TANAKA, Ph.D.

GLAXO WELLCOME REPRESENTATIVES PRESENT:

ARTHUR CIOCIOLA, Ph.D.
ANDREW GUSTAFSON, Ph.D.
DR. DAVE McSORLEY
WALTER PETERSON, M.D.
DUANE WEBB, M.D.
DR. ALICE WEISSFELD
RUSSELL WILLIAMSON, Ph.D.

C O N T E N T S

P R O C E E D I N G S

(8:10 a.m.)

DR. FISHER: I would like to welcome everybody this morning to the joint meeting of the anti-infective drugs group and the GI drugs advisory panel.

I am going to ask first, since this is a combined meeting, for people to go around the table, introduce themselves by name, institution, and committee. I am going to ask Dr. Fredd to start.

DR. FREDD: I am Steve Fredd. I am with the FDA, Director of the Division of Gastrointestinal and Coagulation Drug Products.

DR. MEGRAUD: I am Francis Megraud from the University of Bordeaux in France.

DR. LAINE: Loren Laine, gastroenterology, USC School of Medicine, Los Angeles.

DR. McQUAID: Ken McQuaid, gastroenterology, the University of California in San Francisco.

DR. WALSH: I am John Walsh, University of California, Los Angeles.

DR. RELLER: Barth Reller, infectious diseases and clinical microbiology, Duke University.

DR. BERTINO: Joseph Bertino, Bassett Health Care, Cooperstown, New York, Anti-infective Subcommittee.

DR. NORDEN: Carl Norden, infectious disease, Cooper Hospital, University of New Jersey Medical School.

DR. KIRSCHNER: Barbara Kirschner, pediatric gastroenterology, University of Chicago.

DR. FISHER: Rosemarie Fisher, Yale University, GI advisory.

DR. CRAIG: Bill Craig from the University of Wisconsin and the Veterans Administration in Madison, Wisconsin, the anti-infective advisory group.

MS. McGOODWIN: Ermona McGoodwin, the Executive Secretary for the Anti-infective Committee.

DR. COMER: Gail Comer, GI advisory, State University of New York, Stony Brook.

DR. DUNN: Kay Dunn, statistical consultant, Baylor College of Medicine.

DR. BUTT: Jim Butt, gastroenterology, University of Missouri, Columbia.

DR. JUDSON: Frank Judson, infectious diseases, University of Colorado and Denver Health and Hospitals.

DR. BANKS-BRIGHT: Virginia Banks-Bright, the Anti-infective Committee, infectious diseases, Northeast Ohio University College of Medicine, Rootstown, Ohio.

DR. ELASHOFF: Janet Elashoff, Cedars-Sinai and UCLA, GI Drugs Committee.

DR. FANNING: Mary Fanning, FDA. I am the Director of the Anti-infective Drug Products Division.

DR. HOPKINS: Robert Hopkins, medical officer, Anti-infectives, FDA.

DR. MOLEDINA: Nasim Moledina, medical officer, Anti-infectives.

DR. UTRUP: Linda Utrup, microbiologist, Anti-infectives.

DR. FEIGAL: David Feigal. I am the acting Office Director for the Office of Drug Evaluation IV.

DR. FISHER: I would like to thank everybody on the committee, especially for getting themselves together and getting here within short notice after our last meeting. Thank you.

Dr. Fanning, would you like to make some opening remarks as per our agenda?

DR. FANNING: Sure. I will just make them from here if that is okay.

I would also like to thank people for convening so shortly after our last meeting. I am looking forward with trying to deal with some real issues around applications when our last meeting was one that was a bit more theoretical and around the general issues about H. pylori therapy.

I would like to welcome some new members of the Anti-infective Committee. Bill Craig is our new Chair, and we would really like to welcome you, Bill. We are thrilled to have you. Carl Norden has also joined us as a new member. Welcome.

I would like to welcome back two of our old members, Dr. Reller and Dr. Judson, who have joined us as special consultants today to carry on with these discussions.

I think that is really all that I would like to say. We have a full agenda today, and we should probably get on with that.

DR. FISHER: Let me just point out who the guests of the joint committees are. Dr. Megraud, Dr. Laine, Dr. McQuaid, and Dr. Walsh are here as the guests of the committee as consultants.

Ms. McGoodwin, if there is a conflict of interest statement to be read?

MS. McGOODWIN: Thank you, Dr. Fisher.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information

provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. 208(b)(3), full waivers have been granted to Drs. Gail Comer and Rosemarie Fisher. A copy of these waiver statements may be obtained by submitting a written request to FDA's Freedom of Information Office located in room 12A-30 of the Parklawn Building.

We would also like to disclose for the record that Dr. Butt was previously involved in studies involving ranitidine and omeprazole for indications unrelated to the combination products coming before the committee for consideration.

In addition, Dr. Elashoff was previously involved in a study involving ranitidine for an indication unrelated to the combination product coming before the committee for consideration.

With respect to FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Kenneth McQuaid would like to disclose for the record that he is a principal investigator on a study sponsored by Abbott Laboratories of clarithromycin. Further, in the past he was a principal investigator in a multicenter study sponsored by Glaxo Wellcome on ranitidine bismuth citrate and he has been a speaker for Abbott Laboratories.

Dr. John Walsh would like to disclose that he previously participated in a multicenter trial sponsored by Glaxo Wellcome for patients with Helicobacter pylori.

Dr. Loren Laine reported that he has a research grant from Abbott for a study of omeprazole, amoxicillin, and clarithromycin therapy for Helicobacter pylori.

Dr. Francis Megraud would like to disclose that he was previously involved in a study of clarithromycin for Abbott Laboratories and ranitidine for Glaxo Wellcome. Dr. Megraud has also received speaker fees from these firms.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask

in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. FISHER: Thank you.

I would like to start with the day's session. You can see by the agenda we have a really quite packed day. We are going to try to stick to the timetable that we have outlined here. I would just like to ask members of the committee to hold any questions until each one of the presentations that are on here.

We are going to proceed then at first with the presentation from Abbott on clarithromycin with omeprazole. Dr. Pizzuti?

DR. PIZZUTI: Good morning, ladies and gentlemen. I am pleased to be here on behalf of Abbott Laboratories to present data in support of the use of clarithromycin and omeprazole for the treatment of H. pylori ulcer disease.

The presentation today will clearly show that clarithromycin in combination with omeprazole is indicated for treatment of duodenal ulcer, eradication of H. pylori infection, and prevention of duodenal ulcer recurrence.

In support of this proposed labeling, today's

presentation will consist of the following discussion: in vitro activity, monotherapy pilot trials with clarithromycin, pharmacokinetics, combination therapy studies which include data on efficacy, safety, and resistance, and conclusions.

In the quest to eliminate disease due to H. pylori, a number of agents have been tested for in vitro activity. This slide summarizes the anti-H. pylori activity of a number of agents, including antibiotics and non-antibiotics. What we see here is that clarithromycin is extremely active with an MIC 90 of .015 or less, but we also see that other non-antibiotics do have some anti-H. pylori activity.

One variable, however, which has a major impact not only on the growth of the organisms but on the efficacy of antibiotics, is pH. This slide shows the activity of clarithromycin against H. pylori at various pH. We see here that clarithromycin is still very active at pH 5.5 and is extremely active at pH 8.3 and therefore will be particularly effective if the micro environment, as is suspected with H. pylori, is relatively high in pH.

These data also suggest that the combination of clarithromycin with a strong acid suppressant should produce a favorable outcome. However, before attempting to

combine clarithromycin with acid suppressants, we felt it was necessary to establish its efficacy as monotherapy in order to provide a comparison later.

This slide shows the results of two monotherapy pilot trials in which we evaluated the efficacy of clarithromycin and its ability to eradicate H. pylori in asymptomatic subjects. In these two trials, we evaluated doses of clarithromycin of 1 gram a day divided four times and two times and 2 grams a day also divided four times and two times. The treatment duration was for 2 weeks, and what we see is that we are able to achieve monotherapy eradication rates, at least in these trials, of up to 54 percent.

But one thing that we did notice was that for the same given daily dose, more frequently divided regimens seem to produce better results both for 1 gram and 2 grams. But we also began to notice with higher daily doses that we started to see some increases in adverse events.

Therefore, our objective as to ultimately choose a dose of clarithromycin which would combine the best aspects of efficacy, safety, and also facilitate patient compliance. So, we ended up choosing 500 milligrams t.i.d.

Now, although these results shown on the slide

are among the highest reported for monotherapy, I think we would all agree that eradication rates in this range are probably inadequate to successfully treat H. pylori these days. Therefore, we attempted to combine clarithromycin with acid suppressant agents which would increase eradication rates above these levels, not pose any problems for safety with the combined regimen, and still facilitate patient compliance.

We decided to look at proton pump inhibitors because they are extremely effective in maintaining pH in the range of 5 or greater, but we also discovered, when we combined clarithromycin with omeprazole, a particularly favorable set of interactions. This slide summarizes the pharmacokinetic analyses we undertook in a single study in which we combined clarithromycin 500 milligrams t.i.d. and omeprazole 40 milligrams once a day at steady state. We looked at plasma clarithromycin concentrations, gastric tissue clarithromycin concentrations, plasma omeprazole concentrations, and serial intraluminal gastric pH measurements.

When we first looked at the effect of omeprazole on clarithromycin plasma concentrations, we see the results shown in this slide. Clarithromycin concentrations in the presence of omeprazole are shown in

the yellow line and clarithromycin alone is in pink. We see only marginal enhancement of clarithromycin plasma concentrations when the combination is used. Although there are statistically significant differences in Cmin and AUC, they are probably not clinically significant.

So, while this marginal enhancement is encouraging when the combination is used together, the full picture of the potential for the combination is shown when we evaluate gastric tissue.

This slide shows concentrations of clarithromycin with and without omeprazole in gastric fundus, gastric antrum, and gastric mucus. Once again, clarithromycin in the presence of omeprazole is in the yellow lines and clarithromycin alone is in pink. We see in the gastric fundus only a marginal enhancement of clarithromycin concentrations. In the antrum, however, we see a twofold increase in clarithromycin concentrations at peak, and this may be important since that is usually the site of the heaviest infection with H. pylori, but probably most dramatically we see a 10-fold increase in clarithromycin concentrations in gastric mucus up to the range of 40 micrograms per gram of material studied. This is clearly more than enough to facilitate antimicrobial activity and, once again, is probably most important

because this is the micro environment in which H. pylori exists. Thus, the beneficial effects of omeprazole and clarithromycin are particularly advantageous in the case of H. pylori infection.

Now, we also looked at the effect of clarithromycin on omeprazole concentrations. Once again, here we show the combination, but again these are omeprazole concentrations in yellow and omeprazole alone in light blue. We see higher increases when the combination is used alone and in fact see essentially a doubling of the AUC for omeprazole in the presence of clarithromycin.

Now, although omeprazole alone is very effective in raising pH, essentially doubling the AUC gives us additional assurance that most patients will achieve successful pH levels for eradication of H. pylori.

We did evaluate serial pH measurements in these subjects. This slide shows the mean 24-hour gastric pH, first of all, in patients at baseline prior to receiving any medication, which is in the white line here, and then clarithromycin alone, again in pink, is not expected to have an effect on pH. Omeprazole alone is in light blue, and we see that that maintains pH levels in the range of 5 for most of the 24-hour period and then, with the combination, slightly higher levels as seen in the yellow

line, again just slightly above the levels for omeprazole alone. These data give us additional comfort that clarithromycin can maintain its activity despite the location of H. pylori in the stomach.

All these results then provide several reasons to combine these two agents in well-controlled clinical trials.

This slide summarizes the rationale for the use of clarithromycin with omeprazole for the treatment of H. pylori. First of all, omeprazole alone is a potent anti-secretory agent which promotes ulcer healing. Secondly, clarithromycin in vitro activity is enhanced at higher pH in the presence of omeprazole. Third, clarithromycin concentrations in gastric mucus and gastric tissue are increased by omeprazole, and clarithromycin enhances omeprazole plasma concentrations.

We then began a series of well-controlled clinical trials. We employed a randomized, double-blind, placebo-controlled, multi-center design. Our efficacy endpoints were ulcer healing, eradication of H. pylori, and ulcer prevalence, which accounts for both unhealed as well as recurrent ulcers.

Now, the quality of these endpoints, however, is directly related to the rigor of your assessments. The

methods we chose to assess these endpoints were objective and are shown on this slide.

Endoscopy was used to visually confirm the presence of duodenal ulcer as well as to take tissue samples. It was scheduled five times during the trial and is particularly essential at later time points to discover asymptomatic ulcers. Unscheduled visits were also allowed at intermediate times if symptoms warranted.

The presence or absence of H. pylori was assessed by using three tests concurrently: histology, culture, and urea breath test. As my colleague, Dr. Craft, presented to this committee at its last meeting, eradication is extremely hard to prove. We feel all three tests are necessary in order to prevent false negatives and also prevent falsely high eradication rates. In our studies we were able to confirm all negative results 96 percent of the time with all three tests.

In addition, as Dr. Craft also mentioned, when we looked at single test's predictive value, we saw up to 25 percent false negativity rates if one test is used alone. Thus, this methodology assures us that a negative result is truly negative.

This rigorous methodology became a significant undertaking when you consider the scope of these trials.

This slide shows patient enrollment for two U.S. trials which had three arms and two ex U.S. trials which had two arms. Nearly 900 patients were enrolled prospectively in these trials.

Starting with the U.S. studies, this slide describes the dosing regimen we employed. As you can see, the trials used the required factorial design and therefore had three arms. The first group received clarithromycin 500 milligrams t.i.d. and omeprazole 40 milligrams once a day for the first 2 weeks followed by omeprazole 20 milligrams a day for the last 2 weeks. Group II was essentially omeprazole monotherapy with clarithromycin placebo, and group III was clarithromycin monotherapy with omeprazole placebo.

Now, along with assessing the endpoints using the rigorous methodology mentioned before, timing is also important. This slide shows the evaluation time points we used in these trials.

During the treatment phase, we evaluated patients pre-treatment for the presence or absence of duodenal ulcer and H. pylori. We looked during treatment for symptoms and post treatment, which was the first time we assessed ulcer healing. As my colleague, Dr. Craft, also presented in October, this time point is particularly

good to first assess healing but may be too early to assess eradication because the anti-ulcer therapy can suppress the growth of H. pylori below detectable levels.

In the follow-up phase, we evaluated patients 4 to 6 weeks post therapy, which was the first eradication time point, and then 3 months and 6 months for both eradication and endoscopy.

In addition, as I mentioned before, patients were seen in between these time points if symptoms warranted.

This slide shows the patient accountability for the first trial, M93-100. The first line shows the patients enrolled and then the second line, the patients eligible. In order to be eligible, you had to have H. pylori and you had to have a duodenal ulcer. But as you can see, very few patients were ineligible for evaluation.

The last four lines show the number of patients who were evaluated at each of the subsequent time points, 0 to 5 days, 4 to 6 weeks, 3 months, and 6 months post therapy. We can see that comparable numbers of patients were evaluated at each time point and there were few dropouts throughout the 6 months of the study.

This slide presents the same data for the second U.S. trial, M93-067. Once again, very few of the

enrolled patients were ineligible, and comparable numbers of patients were seen at each of the subsequent time points.

The first efficacy parameter is ulcer healing. As expected, omeprazole alone was very effective in healing ulcers in this patient population, and we see here the data from both studies for all three groups. Omeprazole alone healed ulcers 88 and 85 percent of the time, and the combination of clarithromycin and omeprazole gave results slightly higher, 94 and 88 percent, but these results were not statistically significantly different than omeprazole alone.

We had, however, higher than expected healing rates with clarithromycin alone, 64 and 71 percent, but these results were statistically significantly worse than with the combination.

The second efficacy endpoint was H. pylori eradication which tells a different story for omeprazole alone. Once again, we presented data from both trials here at the 4 to 6-week and 3-month time point. As expected, omeprazole alone does not eradicate H. pylori, and clarithromycin provides moderate eradication rates in the range of 31 to 40 percent, which these data are consistent with the monotherapy trials that I presented earlier.

However, the addition of clarithromycin to omeprazole, when assessed by all three tests, provided higher eradication rates ranging from 64 to 75 percent depending on the time point evaluated. And these results were statistically significantly superior to either of the monotherapy arms.

The third efficacy endpoint was ulcer prevalence which accounts again for all unhealed and recurrent ulcers. Obviously, the objective here is to have as low a number as possible. When we used this stringent methodology -- and I remind you that there were no intervening treatments in the time period from the end of the 28 days up to the 6-month evaluation -- as expected, the omeprazole-alone arm was ineffective in preventing recurrences at this time point. 73 and 77 percent of patients still had ulcer disease at this time point.

However, the addition of clarithromycin to omeprazole improved these prevalence rates by 21 to 47 percent if we just take the difference, 47 here and 21 there, between the two groups. These results were statistically significant.

Clarithromycin alone also provided intermediate prevalence rates between omeprazole and the combination arm.

These data emphasize the importance of a 6-month long-term follow-up and the need to document the bactericidal activity and essentially the maintenance of eradication in these patients, as well as the need to look for asymptomatic ulcers.

If we look at this in a Kaplan-Meier presentation, we see that the combination arm, again shown in yellow, is statistically significantly superior to each of the monotherapy arms, and for the second study, we also show statistical superiority over the combination across the 6-month period compared to each of the monotherapy arms.

If we now look at recurrences by H. pylori status, we see the results on this slide, and again we present the results for H. pylori positives and H. pylori negatives for both trials for all three groups.

As is expected, for H. pylori positives, we have a relatively high recurrence rate, ranging from 33 to 74 percent, which is consistent with what we read in the literature.

The H. pylori negatives, however, usually give much lower recurrence rates and we see that for clarithromycin alone, they are up to 17 percent; for the combination alone, 6 percent in one trial. However, we did

see 39 percent H. pylori negative recurrences in that trial M93-067, which is definitely an outlier among what we would expect and suggests that at least sometimes recurrences may not be due to H. pylori.

The fact that this finding was an outlier was confirmed when we analyzed our European trials. This slide describes the dosing regimen for these trials. There were two European studies.

The first study, M93-058, was identical to the U.S. design in duration and dosages except for the absence of a clarithromycin-alone arm. Patients still received 500 of clarithromycin, 40 milligrams of omeprazole for the first 2 weeks, and 20 milligrams of omeprazole for the second 2 weeks.

The second ex U.S. study used a higher dose of omeprazole, 40 milligrams, just for the last 2 weeks.

As with the U.S. trials, timing of assessments is also important. These are the evaluation time points used for these trials. The treatment phase assessments are identical to what was done for the U.S. trials and the differences that we see in the follow-up phase are only that we omitted the 3-month evaluation and for one trial, 812b, we added a 12-month evaluation.

The accountability for the first trial is shown

here. Study 058 was done in 12 countries, 11 in Europe and New Zealand. We see again that very few patients who were enrolled in this study were ineligible for evaluation and that we have very good follow-up throughout the 6 months of the trial.

This is the same data for study 812b, which again shows very high rates of eligibility and also very good follow-up even at 12 months.

Once again, the first efficacy endpoint was ulcer healing, and the data here are consistent with what we saw in the U.S. trials. Omeprazole alone was very effective in healing ulcers, providing healing rates of 95 and 99 percent, and the addition of clarithromycin to omeprazole produced slightly higher results with 99 percent and a perfect score in 812. However, these differences are not statistically significant.

The second endpoint again was eradication which tells a different story once again for omeprazole alone. As we expected and as we saw in the U.S. trials, essentially no one was eradicated by omeprazole alone, but the addition of clarithromycin to omeprazole provided slightly higher rates of 74 to 83 percent in these trials. Again, this was done using all three methods of assessing the presence of H. pylori.

And the third efficacy endpoint again was ulcer prevalence and we saw very consistent results between these two trials such that for the patients who took omeprazole alone, 55 percent at 6 months in both trials and 77 percent at 12 months still had ulcer disease in these trials. The addition of clarithromycin to omeprazole improved these rates by 43 to 73 percent such that 96 percent of those patients in 812b were essentially cured of ulcer disease by 12 months.

Looking at the Kaplan-Meier curves for these trials, again we see statistically significant superiority for the combination over the monotherapy arm for the first trial and the same statistical superiority in the second trial, this time over 1 year of follow-up.

Ulcer recurrences by H. pylori status are shown on this slide for the ex U.S. trials. Once again, as expected, we have a fairly high recurrence rate for the Hp positives, but also as expected, we see very few recurrences for Hp negatives, a maximum of 6 percent, which further confirms that the result in the second U.S. trial was an outlier.

Now, with respect to clinical symptoms, the combination of clarithromycin and omeprazole also provided statistically significant superiority in resolution or

improvement of three key parameters when evaluated at the 6-month time point. This slide shows resolution or improvement in epigastric pain, daytime abdominal pain, and nighttime abdominal pain for both the U.S. and the ex U.S. studies. For each of these symptoms for each of the studies, there was statistically significant improvement in the combination compared to omeprazole alone. These data are also consistent with the objective findings presented earlier.

So, to summarize the efficacy results of all of the well-controlled trials, we see that clarithromycin in combination with omeprazole heals duodenal ulcer, eradicates H. pylori reliably with an average eradication rate of 75 percent, prevents ulcer recurrence, and improves ulcer symptoms when compared to omeprazole alone.

Susceptibility is routinely assessed in all anti-infective clinical trials and those for H. pylori ulcer disease should be no different.

This slide shows the in vitro clarithromycin susceptibility of the pre-treatment isolates obtained and evaluated in central laboratories in both the U.S. and Europe. As we can see, regardless of how we express it, whether it is MIC 50 or 90, the results are very similar regardless of location, with essentially a one tube

difference between the MIC evaluations.

Expressed another way, if we take a breakpoint of less than or equal to 2 micrograms per ml as susceptible, 95 percent of the U.S. isolates and 99 percent of the European isolates were susceptible to clarithromycin.

Now, in spite of these very high susceptibility rates and the efficacy of clarithromycin, its bactericidal activity leads by definition to the development of some resistance. This slide shows the H. pylori post-treatment susceptibility for any isolates obtained at any time in the follow-up of these trials. What we show here are only patients who had pre-treatment susceptible isolates.

So, we see 126 in the U.S. and 118 patients in Europe who had susceptible isolates at baseline, and 31 patients in the U.S. and 15 in Europe had isolates obtained after therapy. In the U.S. 26 out of those 126 patients developed resistant isolates and in Europe 10 out of 118 developed resistant isolates. This approximate rate of 10 to 20 percent of patients who developed resistant isolates is consistent with our 75 percent eradication rates and also shows that results in the U.S. and Europe are similar.

We do not know the implications, however, for subsequent treatment for H. pylori eradication of these

individuals, and we have no evidence that these isolates are more or less easily transmitted person to person. We have seen, however, 15 resistant isolates revert to susceptible after continued follow-up which suggests a possible selective disadvantage for the resistant phenotype.

We are aware that the committee may address a question of microbiological breakpoints today, and the question may be can we establish breakpoints for H. pylori and if so, what should they be. If the committee decides that breakpoints need to be set today, we respectfully request that we be allowed to present some additional data which are pertinent to that discussion at that time.

Safety was assessed in all of our trials using laboratory tests, physical examination, and collection of adverse events. In the well-controlled trials, there were no clinically significant laboratory abnormalities related to study drug and no clinically significant differences in physical examinations seen in these patients. There were no serious adverse events reported and very few patients, 3 percent, dropped out of the study due to adverse events.

A synopsis of the most frequently reported adverse events is shown here. When we evaluate the data provided from the combination, omeprazole alone, and

clarithromycin alone, which was derived from the U.S. studies, we could see that there is no difference in the profile of clarithromycin with omeprazole compared to clarithromycin alone.

In addition, compared to our historical database, we see here that there are no differences in the profile with clarithromycin three times a day compared to what we know in the clinical trials for two times a day. Also we see that the profile here suggests no surprises compared to what we know about the post-marketing safety of clarithromycin which comprises over 100 million uses of the compound, nor do we see any surprises when we take into account the post-marketing safety profile for omeprazole.

In conclusion, clarithromycin is highly active in vitro and in vivo against H. pylori. It has a unique concentration profile in gastric tissue and gastric mucus which is enhanced by omeprazole. And in well-controlled clinical trials, both in the U.S. and outside the U.S., the combination of clarithromycin with omeprazole reliably heals duodenal ulcer, eradicates H. pylori, prevents ulcer recurrence, and improves ulcer symptoms compared to omeprazole alone.

Thank you for your attention.

(Applause.)

DR. FISHER: Thank you, Dr. Pizzuti.

Questions? Dr. Craig?

DR. CRAIG: You provided data on the MICs for clarithromycin. Since we are interested in eradication, do you also have MBC data for clarithromycin? Is it very similar to the MIC or are much higher concentrations required to kill the organism?

DR. PIZZUTI: Let me ask Dr. Tanaka.

It is very similar.

DR. FISHER: Dr. Norden?

DR. NORDEN: David, I am concerned about the resistance issue. It is true that if you start with the total number of patients enrolled or eligible, that your resistance prevalence is not terribly high, but virtually all or close to all of the patients who failed do have resistance. And I think that has to be a concern. If you do have other information about what happens afterwards, I think it would be useful because I think this would concern everybody on the committee.

DR. PIZZUTI: We do not have any follow-up data in these patients, subsequent treatment data, because there were very few of these patients in all of the trials where we obtained the isolate and it was resistant. We will attempt to get that, though.

DR. FISHER: Is everybody awake?

(Laughter.)

DR. FISHER: Dr. Fredd?

DR. FREDD: Could you tell me the formula by which you calculated your eradication rates? Was it all Hp positive people who converted, all Hp positive who healed? What was the denominator?

DR. PIZZUTI: I believe everybody in the trial had to have H. pylori present, so everybody that made it to the eradication point was evaluated and that was the ratio, the number that had no H. pylori over the number that were evaluable at that time point.

DR. COMER: This is whether they were healed or not. Correct?

DR. PIZZUTI: I will ask our statistician to provide the precise answer.

DR. SIEPMAN: Nancy Siepman, Abbott Labs.

No. It is as good in the unhealed patients. However, we only have 13 unhealed patients within the whole four studies.

DR. FREDD: But they had to have made it to the evaluable point.

DR. PIZZUTI: Right.

DR. FREDD: They did not have to take a certain

amount of medication?

DR. PIZZUTI: We had a very good compliance rate.

DR. FREDD: But that was not a requirement.

DR. PIZZUTI: Yes, I believe it was. They had to take greater than 60 percent.

DR. FREDD: If you take all Hp positive people, whether they took all the amount of medication, whether they healed or whatever, what in that whole cohort was the eradication rate? Was it different than what you presented?

DR. PIZZUTI: We will have that in one minute.

DR. FISHER: While we are getting that, maybe we can get another question. Dr. Elashoff?

DR. ELASHOFF: It is not a question. It is just a statement that the medical officer intent-to-treat versions of the eradication rates are not the same. They are lower.

DR. FISHER: Dr. Laine?

DR. LAINE: Your 36 of 46 post-treatment isolates being resistant, that was for either clarithromycin or omeprazole plus clarithromycin?

DR. PIZZUTI: No. That was for the combination.

DR. LAINE: What is the data on the clarithromycin monotherapy? Is there a difference when you just consider as the denominator those post-treatment isolates that are available?

DR. PIZZUTI: For the clarithromycin-alone arms? It is essentially the same ratio.

DR. FISHER: Dr. Bertino?

DR. BERTINO: In your eradication or lack of eradication subjects, were there any characteristics in terms of were there more smokers, any sex differences, things like that, potential explanation other than resistance patterns?

DR. PIZZUTI: We evaluated that and collected that information in the trials and did not see any difference in response rates whether they be recurrence rates or H. pylori eradication for the demographic parameters.

DR. CRAIG: It seems like from your biopsies you did a grading system that also tended to reflect the number of H. pylori organisms seen. Was there any correlation with having a larger number of organisms having a larger failure rate?

DR. PIZZUTI: No correlation. We do have the data that was requested by somebody previously.

DR. FISHER: Dr. Fredd.

DR. PIZZUTI: Dr. Fredd, okay.

This is the intent-to-treat eradication rates for all four of the trials which again are slightly different but fairly comparable and statistically significant regardless of how you look at it.

DR. LAINE: If it is intent to treat, why do the numbers change from 6 weeks to 3 months?

DR. FREDD: It is not the randomized population. How many did you have initially randomized in each of the groups? They were all Hp positive to begin with. What was the number randomized in each of the groups, and why are we seeing 64, 62, and 48?

DR. PIZZUTI: Let me have the statistician comment on the different denominators in the groups.

DR. SIEPMAN: Dr. Fredd is correct. Those are not all randomized patients, and we do have an all-randomized patient analysis which is coming. Those are the patients who had the data available. We included all the patients who had data available. So, the difference between 4 to 6 weeks and 3 months analysis is because patients who had unhealed ulcers or recurrence before 4 to 6 weeks withdrew. Therefore, it is not included in the 3-month analysis.

DR. PIZZUTI: So, if they failed, they were excluded from further time points.

DR. FISHER: Is it failed or is it just data not available? Because the clarithro plus omeprazole group eligible was 73 patients and we are down to 67 at 3 months. We are saying we have basically 16 patients with no data or cannot evaluate, but again is that an intent to treat?

DR. PIZZUTI: For this particular analysis, again as the statistician mentioned, people that had recurrences were excluded from later time points, so you see a drop from the 4 to 6 weeks to the 3 months, and you also exclude people that did not heal, so that takes off a few, or anybody else that was unavailable during that time period for an analysis where they dropped out for other reasons, whether it be lost to follow-up, adverse events.

This slide shows, again for the first trial, the different intent-to-treat evaluations. Now, the difference between intent-to-treat 1 and 2 was that everybody in intent-to-treat 2 who even failed to come back is considered a failure, and that is not what we know to be the case but it is the absolute worst case analysis that we could do. Again, we see the rates are a little bit lower for the eradication, but I think this accounts for all the lost-to-follow-ups regardless of cause. We know many were

lost to follow-up because they healed.

DR. FISHER: Dr. Temple?

DR. TEMPLE: I guess it shows that it is important to keep terminology precise. We actually contributed to this in some of our guidance by calling an all patients with data analysis an intent-to-treat analysis, but that is not really true. A true intent-to-treat is rarely done outside of mortality trials. Maybe it should be done more.

But these are really all patients with data analysis, and that last analysis, while you can call it an intent-to-treat, is really a worst case assuming all patients without data are unhealed. I guess it is just very important to say what each analysis is and not use a buzzword, otherwise no one will know what anybody is talking about.

DR. FISHER: That is an absolute fact.

(Laughter.)

DR. FISHER: Any other questions? Dr. Reller?

DR. RELLER: In the U.S. trials, those persons who had persistent H. pylori in the combination therapy versus clarithromycin alone, what are the relative proportion of resistant strains in those two groups?

DR. PIZZUTI: We saw relatively similar rates.

What we presented to you in the main presentation was in the combination which was 26 out of 31 isolates showed resistance post treatment, and there were 126 starting who were evaluable and had susceptible isolates. The results for the clarithromycin-alone arm were similar to that in that the ratio of resistant isolates to the number recovered was about the same post treatment.

DR. RELLER: The reason I ask is based on the pharmacodynamic data earlier, theoretically the combination group was exposed at least in the mucus to a much higher concentration of clarithromycin. Do you have in vitro data as to the killing activity of clarithromycin as a function of concentration for susceptible organisms?

DR. PIZZUTI: We do have that data. It will just take us a minute to locate the slide.

DR. MOLEDINA: I guess most of the questions that have been asked by the members can be addressed by the FDA presentation. So, I think if you can wait for the FDA to present and then ask the questions, I think it would be more appropriate.

DR. FISHER: Okay, and then we can have a little back and forth, if we can, at that point.

DR. PIZZUTI: We have the answer for Dr. Reller's question right now, if we could just quickly

answer that.

DR. FISHER: Why don't we do that right now and then let's try to save any statistical things until the FDA presentation?

DR. PIZZUTI: So, this is the effect of pH on the different kill kinetics, ranging from 6.5 to 8.

DR. RELLER: That wasn't the question. We will wait for the FDA.

We are aware of the effect like with erythromycin of pH on killing. The question was, is there better killing at a higher concentration of clarithromycin versus a lower when the lower is still within the susceptible range? Do you get better eradication when you exceed by some margin of killing with clarithromycin? Because theoretically in the omeprazole-clarithromycin group, those organisms were exposed to that higher concentration compared with the clarithromycin alone.

DR. PIZZUTI: Are you talking about in vitro data or in vivo correlation with serum levels?

DR. RELLER: What I wanted to find out is whether the in vitro data matched the clinical trial results.

DR. CRAIG: I think what he is looking for is concentration-dependent killing.

DR. RELLER: Exactly.

(Laughter.)

DR. TANAKA: Ken Tanaka, Abbott Laboratories.

Dr. Reller, we have one example where we have tested by concentration the killing effect, and it is clear that killing is concentration-dependent, that the rapid killing can occur at higher concentrations despite whatever change we have with pH. So, for instance, at .12 micrograms per ml, we get decreased killing at pH 6.5 compared to 8. At 3 micrograms per ml, we get as rapid killing compared to a pH 8 effect. So, the higher concentration would give us better killing response in vitro.

DR. FISHER: Dr. Walsh?

DR. WALSH: This may come up later, so tell me if it will. But there seemed to be some discrepancy between the improvement of symptoms and rate of eradication in that the symptoms at 6 months were especially good in the clarithromycin-alone category. Is that broken down, the symptoms of eradication versus no eradication, in the different groups? I know they correlated.

DR. PIZZUTI: We can obtain that very quickly. Again, the clarithromycin --

DR. FISHER: Dr. Elashoff?

DR. ELASHOFF: The sample size is pretty small.

DR. CRAIG: That is true.

DR. PIZZUTI: This includes other symptoms besides the ones that we presented, but the clarithromycin-alone arm was also allowed to receive antacids for symptomatic relief too, but no acid suppressant drugs.

DR. COMER: Just a point of clarification. Even the clarithromycin-alone groups were treated for 2 weeks with omeprazole.

DR. PIZZUTI: No. They had just clarithromycin for the first 2 weeks and omeprazole-placebo for the entire 4 weeks.

DR. ELASHOFF: It is the wrong slide. That is the problem.

DR. COMER: No. The clarithromycin group received clarithromycin alone for 2 weeks and then 2 weeks of omeprazole 20 milligrams a day. Is that correct?

DR. PIZZUTI: No. No omeprazole at all.

DR. WALSH: Do you have that slide for clarithromycin alone?

DR. PIZZUTI: There is no difference between the H. pylori positives and negatives for that slide with clarithromycin, but we do not have it here.

DR. FISHER: If there are no other questions

from the group, we will go on to the FDA's presentation. Dr. Moledina?

DR. MOLEDINA: I am Dr. Moledina, the medical officer for this application.

Before I start my presentation, I would like to mention that all the evaluability criteria that Abbott used in all the four pivotal studies, I used the same evaluability criteria, all the evaluable patients at each time point that Abbott had in the application. My numbers did not change.

I would like to give credit to Dr. John Senior, the medical officer in the GI Division, who verified the endoscopic results for me, and Ms. Beth Turney, a statistician, who sort of constructed all the efficacy tables for me.

As you heard from Abbott, they did four double-blind, randomized, well-controlled studies. Two of them were conducted in the U.S. and two in European countries.

The study 92-812b was a study that used a higher dose of omeprazole during the maintenance phase. That is why I am not going to sort of present that study as part of my efficacy analysis. All I am going to do is present the two U.S. studies and one European study which also did not have the clarithromycin-alone arm, and that

was because the European IRBs did not find it ethical to use clarithromycin alone.

The sponsor is requesting the following indication and proposed dosage recommendation in the package insert. The indication that they are looking for is treatment of active duodenal ulcer and prevention of duodenal ulcer recurrence associated with Helicobacter pylori infection in combination with omeprazole.

The dosage recommendation is a 28-day treatment therapy combining clarithromycin 500 milligrams t.i.d. plus omeprazole 14 milligrams once a day for the first 14 days and then the maintenance phase in which omeprazole will be given at 20 milligrams once a day.

Abbott already presented the details of all the studies. The way that they had looked at the data was they looked at the ulcer healing in all those patients that were eligible or that were evaluable for efficacy, and those were the patients who had H. pylori infection at baseline and had an ulcer at baseline. They looked at ulcer healing at several time points, evaluation time points, which was at post therapy, at 4 to 6 weeks post therapy, at 3 months, and at 6 months in the U.S. studies, and the European studies had slightly different time points where evaluation was made for efficacy. Then they looked at eradication at

4 to 6 weeks, 3 months, and 6 months.

I wanted to choose a time point where I can look at ulcer healing as well as eradication at one time point. My GI colleagues always looked at ulcer healing at the end of therapy, but we cannot look at eradication for H. pylori at the end of therapy. As you all know, if you leave the ulcer alone, it is going to heal by itself as it is. So, I chose a point 4 to 6 weeks post therapy and looked at one time point evaluation for all these studies.

So, from now on all the data that I am going to be presenting will be looked -- all those evaluation time points are at 4 to 6 weeks post therapy. The slides do not say post therapy, but it means post therapy because I think when I gave my slides to be made, they took the "post therapy" out because they could not fit it in or something.

(Laughter.)

DR. MOLEDINA: So, the first study that I am going to present is the one that does not have very good results, which Abbott presented as the second study, which is 067. In that study, there were three treatment arm groups: clarithromycin/omeprazole, clarithromycin-alone and omeprazole-alone arms.

All I want really the committee to focus on is I will only include those patients that were evaluable for

efficacy who had H. pylori infection and had an ulcer and were evaluable at 4 to 6 weeks. I am going to include those patients.

When you look at the enrollment status, you see that there are almost 80 patients in each group, but patients who were not evaluable at 4 to 6 weeks have been excluded. So, I ended up having a denominator for evaluable analysis where in the clarithromycin and omeprazole group, there were 61 patients, and in the clarithromycin-alone group there were 67, and 64 in the omeprazole.

We had some patients whose Hp status was missing at 4 to 6 weeks, so I called those patients unevaluable. Later on you will see that when I have done my overall success analysis, I have included those patients as being failures. So, my adjusted denominator for the evaluable patients for this particular study, I was left with 56 patients in the clari-omeprazole group.

I would like to focus your attention in the last row of this slide, patients who had no ulcer and were Hp negative by post-treatment week 4 to 6. There were only 59 percent of patients who did not have an ulcer and were eradicated of their H. pylori at the end of 4 to 6 weeks treatment. Compared to the clarithromycin-alone arm, there

are only 18 percent. Of course, none of these patients in the omeprazole arm had Hp negative at the end of 4 to 6 weeks.

So, this is what I am trying to base my overall success rate is.

When you look at the recurrence analysis in this patient population who were Hp negative at the end of 4 to 6 weeks and had no ulcer by endoscopic criteria and take those patients, I want the committee to realize that these are known randomized patients. I have just sort of dropped all those patients who were Hp positive and who had presence of ulcer and took those patients and then looked at the recurrence rate in those group of patients.

Similarly, if you look at the patients who had no recurrence by the end of 6 months, they were only 68 percent of patients in the clari-omeprazole arm. Of course, these numbers are so small because when you look at the denominator used for recurrence analysis for clarithromycin, all these patients had ulcers present. So, I had dropped all those patients. So, there were very few patients in the clarithromycin-alone arm who had no ulcers and who were H. pylori negative also to begin with to assess ulcer recurrence in them.

So, really though the number looks kind of bad

compared to the clarithromycin-alone arm, I think it is not very significant. As you can see, the p values are not significant.

Similarly, if you look at the recurrence analysis in the Hp positive patients, we see a similar pattern. The only difference is that the denominator for the recurrence analysis very, very low in the clarithromycin and omeprazole arm to begin with. Of course, the omeprazole arm has more patients because all of them were Hp positive at the end of 4 to 6 weeks.

So, looking at this, it seems as if once you eradicate the organism at 4 to 6 weeks and you heal the ulcer, no matter what you do afterwards, the recurrence rate is the same for Hp positive and Hp negative patients. So, this is one study that really did -- the ulcer recurrence analysis did not look very good.

But I have two other studies.

You already heard the Abbott data, the evaluation that was done by them in a little different way, but the bottom line is the numbers are the same.

So, when you look at the second study, which is study 100, the tables are identical to the ones that I had presented for study 067. In this study, the number of patients that were evaluable at 4 to 6 weeks post treatment

were ranging from 65 to 68 in the three arms. I would like you to concentrate on this last row, patients who had no ulcer and were Hp negative was 58 compared to that study 067, they were 59 percent of patients. So, really when you look at the overall success rate in both the U.S. studies, though the recurrence analyses look different, the overall success looks the same for both the studies. It was 59 percent for study 067 and 58 percent here.

Now, when you take this group of patients and you look at recurrence, none of these patients recurred, all, 100 percent had no recurrence. So, we are looking at one study that had 68 percent recurrence at 6 months and one study that had 100 percent.

So, the two U.S. studies do not really support each other as far as recurrence data is concerned. But I would like the committee to be aware that the denominators are very small and I have dropped all those patients who were ulcer positive and Hp positive at the end of 4 to 6 weeks.

I get some lower results of no recurrence for patients who are Hp positive. So, this study shows a difference between Hp negative and Hp positive patients when you look at the recurrence rate at 6 months.

I do not know whether the statisticians on the

committee are going to criticize me, but I tried to put these two studies together thinking that though the recurrence data in those two studies do not gibe, one does not support the other, at least the overall success, which is what I call as patients who are Hp negative and had no ulcer at the end of 4 to 6 weeks post-treatment, was the same. So, I tried to put the two studies together just to make the numbers look a little bit better.

Doing that, there were about 77 percent of patients who were evaluable in the clari-omeprazole arm when I combined the two studies. When you look at the status of 4 to 6 weeks post therapy, patients who had no ulcer and were Hp negative by 4 to 6 weeks, it was 58 percent. So, really these numbers do not change because both the studies had about the same percentage.

When you look at the recurrence and you put the two studies together in the Hp negative patients, then at the end of 6 months, we see that patients who had no recurrence was 86 percent. This is because one study had 100 percent and the other 68, and if you combine -- I think the statisticians are going to chew me out.

(Laughter.)

DR. MOLEDINA: But I just wanted to give you an idea that if you do that, it looks very good, but if you

take the study individually, then one does not support the other as far as recurrence is concerned.

This is the combination for the Hp positive patients which is much lower.

This is the European study that had the same dosage regimen as the U.S. studies. The only difference was that there was no clarithromycin-alone arm in the study and they did not have a 3-month evaluation time point. They only evaluated at 4 to 6 weeks and at 6 months.

This European study really shows much better data than the U.S. studies. In that study, there were patients at the end of 4 to 6 weeks post treatment who had no ulcers and were Hp negative. 72 percent of them were included in this group. So, this is the overall success rate in that European study. The U.S. studies had like 58 percent and the European study had 72. So, there is really not that much difference.

I did the recurrence analysis the same way as I did for the U.S. studies, and when you look at the Hp negative patients, 96 percent of them did not recur compared to omeprazole. All these patients still had Hp positive. Of those patients who still had Hp positive, 73 percent did not have no recurrence in the omeprazole arm, while 82 percent did not recur at the end of 6 months.

To really summarize the efficacy data that I have reviewed from the database that Abbott submitted to this NDA, I think that I cannot use the recurrence data that I have since one European study did not have a clarithromycin-alone arm and the two U.S. studies do not support each other.

I think that I can define the endpoint by using overall success, and what I mean by that is overall success is defined as those patients who were evaluable who were infected with H. pylori and had an ulcer pretreatment who subsequently became H. pylori negative and had a healed ulcer at 4 to 6 weeks post treatment.

The results of these two U.S. studies and one foreign study are summarized here. These are the same numbers. The only thing is those 5 patients in this group in this study who we could not verify the Hp status, I called them failures. So, the overall success looks a little -- I would call this like a modified intent-to-treat. It is 2 percentage lower than what we got.

So, when you look at this, you see that if you cure the ulcer and you eradicate the organism at 4 to 6 weeks, this is what you get. You get an overall success rate ranging from 54 percent to 72 percent in the data that was given to me for review.

Safety is really not a big issue with omeprazole and clarithromycin. Both omeprazole and clarithromycin are approved drugs. We know the safety profile. They are already labeled and it is in the package insert. So, it is not a big problem.

I just wanted to give you an idea as to the duration of treatment. Since the sponsor is asking for a 2-week treatment of clarithromycin and a 4-week treatment of omeprazole, I just wanted to let the members know that 92 percent of patients did receive clarithromycin in the recommended dose in the package insert, and 88 percent did receive the dosage that is recommended in the package insert. And we are pretty comfortable with that.

As far as the ADRs are concerned, you already heard Abbott present details. The most common side effect, which is due to clarithromycin, is taste perversion which is just a bad taste in the mouth. When I first reviewed the original NDA for this, there was only 6 percent of patients in a database of about 4,000 patients who had taste perversion, and that is what is in the package insert. But in this particular study, we see a much higher incidence of disturbance of taste. But patients do not become noncompliant, so that is a good thing.

The other side effects are the usual GI side

effects that we see with clarithromycin, but these are patients who were treated with the combination. The profile seems like this is a clarithromycin profile of the ADRs.

If you compare the three arms in the U.S. studies where a total of 498 patients are evaluated for safety, there is really no difference in the report of ADRs in these three groups. When you break it down to the most common ADRs reported, it is still taste perversion, which is mostly seen due to clarithromycin. We saw headache, which is also a labeled ADR.

That concludes my talk.

I would like the advisory committee members and our consultants to give us an opinion as to whether using overall success is appropriate to evaluate and somehow how to write a label. What should we put in the package insert if at all an approval is recommended?

Thank you very much.

(Applause.)

DR. FISHER: Thank you.

Dr. Fredd?

DR. FREDD: Could I ask you, Dr. Moledina? Overall success in terms of the way you figured it out, was that an eradication rate in healed patients who were Hp

positive?

DR. MOLEDINA: Yes.

DR. FREDD: Yes. So, rather than use terminology of overall success, the numbers you are presenting are the eradication rates in patients who were Hp positive to begin with.

DR. MOLEDINA: Yes.

DR. FREDD: Let me ask what I think it is showing.

You have Hp positive patients who had an active ulcer who healed, and in those healed people, you figured out how many converted to Hp negative. Is that right?

DR. MOLEDINA: Yes. I think the terminology can be anything. I just wanted to sort of show you that when you start off with patients who are Hp positive, patients who were infected by the criteria that we have used -- and we have been very strict using that criteria because we needed more than one test to confirm that -- and when you healed their ulcers at the end of 4 to 6 weeks and you take that cohort of patients, this is the kind of eradication rates and success rates that we get.

DR. FREDD: So, it is an eradication in people who healed.

DR. MOLEDINA: Yes, okay.

MS. TURNEY: Can I comment? I am Beth Turney, the statistician.

Overall success includes patients who are unhealed. They are counted as a failure. To be a success, you have to be healed and you have to be eradicated. You are counted as a failure if you were unhealed or you were not eradicated. If one of those was missing and you still were a failure on one of those criteria, you are still counted as a failure. If you were a success on one of those and you were missing on the other one, you were left out of the denominator. This was not an intent-to-treat or a modified intent-to-treat kind of analysis.

DR. FISHER: So, if you were one positive and one negative, you were left out of the analysis?

MS. TURNEY: No. One positive, one negative, you are a failure.

DR. FISHER: So, who did you just say you left out of the denominator?

MS. TURNEY: If you were one positive and one missing, you are left out.

DR. FISHER: Okay.

Dr. Temple?

DR. TEMPLE: The answer to Dr. Fredd's question was no.

MS. TURNEY: Yes.

DR. TEMPLE: It is not the eradication rate in people who healed. It is people who both healed and were eradicated, which is a different number.

One could also ask what is the most relevant question here. Whether an ulcer heals at 4 weeks has a certain random quality to it, and it is not clear why one would want to mix healing and eradication in the same question. You might simply ask what is the eradication rate.

I guess I wondered whether you agree with the sponsor's numbers on what the eradication rates are, which were slightly higher than your overall success rate, not that much.

DR. MOLEDINA: Yes. I do not disagree. They just looked at a different cohort of patients and I looked at it in a different way. I did a much more strict analysis because in our division, when we write the label, we give the indication as -- we have an indication which is an ulcer here which is an active ulcer disease and it is caused by a certain organism, which is H. pylori. Then that is the way we write the label. So, based upon how you write the package inserts, I tried to look at one time point in which it would make some sense.

What the company did was looked at ulcer healing at 5 days post therapy and looked at eradication at 4 weeks post therapy. I just looked at all the patients at one time point.

DR. FISHER: What we are all sort of asking is, if you forgot about whether the ulcer was healed or not healed at 4 to 6 weeks post therapy, what is the eradication of H. pylori?

MS. TURNEY: Can I make a comment here? One problem, we do not know the true eradication rate is because we do not know the Hp status of unhealed patients. By design of the trial, if they were unhealed at the end of therapy, they were dropped from the study. We do not know their eradication rate at 4 to 6 weeks post treatment. So, what do we do with those patients? Do we count them as not eradicated? Do we leave them out of the denominator? What do we do?

DR. FISHER: But you look at them both ways and tell us what those numbers are.

MS. TURNEY: I did a worst case analysis. I do not have a slide for this. Did you make a slide of the worst case analysis?

DR. MOLEDINA: No. But I think the committee has your package. Yes, one of the tables in the

statistician's review because I did send it to the committee.

DR. FISHER: Yes. We do have your review, if you can --

MS. TURNEY: Well, it is in a variety of different places unfortunately.

DR. FISHER: If you can give us a table number, I think we can find it.

MS. TURNEY: Okay. Let's start with table number 7 on page 9 of my review.

DR. FISHER: It is tab 3 and it is page 9 at the top of it, labeled Study 067 Results from Worst Case Analysis of MITT Group.

DR. COMER: Excuse me. We do have the H. pylori status for the unhealed patients at the immediate endpoint. Right? But that is confounded by the treatment. Is that why we are not looking at it?

DR. FISHER: Right.

MS. TURNEY: Yes.

In the worst case analysis, if you did not have the information, you were counted as an unsuccessful outcome. I have defined an -- MITT means modified intent-to-treat group. This group is not all enrolled patients. It is those patients who have an ulcer and who are H.

pylori positive at baseline.

So, if we look at table 7 -- this is for study 067 -- if you look at the second line of the table, patients who were Hp negative at 4 to 6 weeks post treatment, it is 57 percent, 42 divided by 74, for clarithromycin plus omeprazole. Then for clarithromycin, it is 20 percent, which is 15 divided 74, and for omeprazole it is 0 percent, 0 out of 71.

For study 100, a similar table is presented on page 13. It is table 15 of my review. On the second line of this table, for the combination the eradication rate is 43 divided by 77, which is 56 percent. For the clarithromycin arm, it is 17 divided by 82, which is 21 percent, and for omeprazole it is 0 percent, 0 out of 80.

A similar table for study 58 is on page 22. It is table 31. For the combination, the eradication rate was 68 divided by 99, which is 69 percent, versus 4 divided by 104 for omeprazole, which is 4 percent.

DR. FISHER: So, basically in the worst case scenario in the three studies, we have got eradication rates of 57, 56, and 69 with the combination.

MS. TURNEY: Yes, that is correct.

DR. MOLEDINA: Yes.

DR. FISHER: Other questions? Dr. Laine?

DR. LAINE: I was just going to say that I personally as a consultant favor individualizing endpoints such as Hp eradication rather than kind of combining something such as Hp eradication in those who healed in this particular case.

MS. TURNEY: I would like to make one more comment. On these tables, also included is an ulcer-free kind of response. If you were healed at the end of treatment and you did not recur by 4 to 6 weeks post treatment, you were counted as a success. So, it is kind of a cumulative ulcer-free by the week 4 to 6. That is just to clarify that if you were looking at the similar results in those particular tables.

So, again in this worst case analysis, if you had a successful outcome, you are counted as a success. Any other outcome you were counted as a failure or an unsuccessful outcome.

DR. MOLEDINA: I would like to comment on what Dr. Laine said, that to him it did not matter. He wants to look at ulcer healing or eradication separately. But here we are trying to say that H. pylori causes the ulcer. We were trying to connect this disease with an organism. That is why the GI people always think of things a little different than the ID people. That is why I did not try to

repeat what Abbott had presented because their analysis was done separately, and I did not want to sort of rehash whatever they had done. So, I tried to approach it in a little different way.

DR. LAINE: I agree. The point I was making was twofold. One, when you look at ulcer rate 4 to 6 weeks later after people have been off therapy, that is not truly an ulcer healing. That is an ulcer healing plus recurrence. So, not that it was wrong to do it that way, but it is a slightly different question than truly ulcer healing. Last time we all agreed that H. pylori eradication would be a surrogate for decrease in the recurrence of ulcer disease. So, that is why I think that is one important thing to look at alone.

DR. FISHER: I just wanted to add that I agree with that because we are getting back to the idea that we are now looking at a point at 4 to 6 weeks in your analysis, which is a combination thing. If we look at the 6-month analysis -- I would like to just go over because maybe it is the time of day or something, but I am getting confused by all the different analyses and so forth.

DR. MOLEDINA: You haven't seen anything yet.

DR. FISHER: I know I haven't seen anything yet. I saw it in the other paper.

(Laughter.)

DR. FISHER: I am waiting for Dr. Hopkins to try to walk me through this tremendously --

DR. MOLEDINA: I tried to make it simple.

(Laughter.)

DR. FISHER: What I would really like somebody to tell me is, at 6 months, is the incidence of recurrence, overall intent-to-treat, Hp negative? If you become Hp negative at the end of therapy, what is the difference in recurrence of ulcer in those groups? I would like to know that, if somebody could put that to me, even later on, in the three studies.

Dr. Fredd is shaking his head no. I would like to know that.

DR. FREDD: Do you want that by treatment group?

DR. FISHER: Yes.

DR. FREDD: Because you may get at very small numbers there by treatment group.

DR. FISHER: I understand that.

DR. FREDD: Or rather address the question of whether independent of treatment, if yo go from an Hp positive to an Hp negative status, what is the recurrence rate versus staying Hp positive?

DR. FISHER: How about if I say I would like to see both of those just on a single slide, even if it is an overhead or something? Because it is in 20 million places I think in here.

DR. FREDD: Well, I think it is worthwhile to see both to see how the small numbers in the treatment groups may not lead you to reasonable conclusions.

DR. FISHER: That is fine. I would like to see it. It is the sort of KISS theory; it is the "keep it simple, stupid," as far as I would like to see it.

(Laughter.)

DR. FREDD: I had asked Ms. Turney to do an analysis like that. I do not know whether she was able to do that.

MS. TURNEY: I do not have it as a modified intent-to-treat. I do not have that in my review. You have to give me a few minutes to put it together on a table.

DR. FISHER: That is fine. I have no problem. We can go on unless anybody has got any --

DR. MOLEDINA: Yes. I think the company had done that kind of ulcer prevalence. Maybe they can show you.

DR. PIZZUTI: If we understand correctly what

the question being asked was, at 6 months for the intent-to-treat what the recurrence rates were, this shows by Hp negative and positive again the two U.S. studies on the top and then the two foreign studies on the bottom, again just for the combination arm.

DR. FISHER: This is in patients who were evaluable, if I am looking right. Correct?

DR. PIZZUTI: Intent-to-treat.

MS. TURNEY: Can I ask what did you do with patients that had missing values in this table? Did you leave them out of the analysis or are they counted as unsuccessful? That is not intent-to-treat then.

DR. FISHER: Right.

MS. TURNEY: In this discussion it is not.

DR. FISHER: The intent-to-treat to my mind in study 100, if I remember my numbers, or 67 should be like 70 something as opposed to 48. Correct? If I am remembering my numbers?

DR. COMER: They did not have that many patients by the 6-month period because they dropped the people that did not heal.

DR. FISHER: That is what I am saying. I am looking for an intent-to-treat. If you took the patients -- and that is what we are talking about -- who were

enrolled in the beginning and if you count the dropouts as failures, as recurrences, what is the worst case scenario? That is what we are asking again. At least that is what I am asking.

DR. COMER: But if they never healed, then they are --

DR. FISHER: Then they are a failure and that is fine.

DR. COMER: Then they are a recurrence too?

DR. FISHER: Sure. Why not? You did not have a camera down there looking at their ulcer every day to see if they have healed up and then recurred within that 4 to 6-week period or at the end of 6 weeks.

MS. TURNEY: So, can I clarify to see what kind of analysis we want? We want all patients who are H. pylori negative. In order to be called a success, you have to be ulcer-free at 6 months. Everybody else, whether you do not have the data or whether you were unhealed, whether you recurred previously, you are a failure.

DR. FISHER: Correct.

MS. TURNEY: Okay. I will try to work on this.

DR. FISHER: Thank you. Even if we get it after lunch.

(Laughter.)

DR. FISHER: Dr. Temple?

DR. TEMPLE: Just for terminology purposes, that is a special kind of intent-to-treat analysis because you are making the worst possible case.

DR. FISHER: Right.

DR. TEMPLE: Everybody lost.

DR. FISHER: That is what I said. I would like to see the worst case scenario.

Dr. Laine?

DR. LAINE: The other question, though, is, do you want to know what happens after they heal and then do they recur? Or do you want to know everybody who does not heal and/or heals and recurs? Typically we do recurrence after people have healed.

DR. FISHER: After healing, right.

DR. LAINE: That is the kind of thing we clinically are usually more interested in.

DR. FISHER: So, it should be the people who healed.

DR. LAINE: So, you would probably want to say everybody who has an ulcer and is Hp positive at the beginning, who heals their ulcer, and then given that group, what happens I would think, if that is not too confusing.

DR. MOLEDINA: We already did that.

DR. FISHER: I think we are getting things confused.

MS. TURNEY: Unhealed patients? Is that what you want? You want to exclude the unhealed patients.

DR. FISHER: Right.

DR. LAINE: Do you agree with that?

DR. FISHER: Yes. No, because we are looking at recurrence.

MS. TURNEY: The unhealed patients at what time? At the end of treatment.

DR. LAINE: At the end of treatment. Oh, yes, both.

DR. FISHER: One minute. We are getting everybody confused here.

Dr. Temple?

DR. TEMPLE: I am a little puzzled. I understand the analysis, but I am a little puzzled by it because you and Dr. Laine just agreed that you ought to render to Caesar what is Caesar's and to God what is God's.

You made the case that eradication was a matter of interest. You are now getting an analysis that blends a whole bunch of stuff together and focuses on recurrence, which I thought you considered a sort of settled matter.

If you eradicate, you are okay. Of course, in study 67 if you eradicate, you were not okay, but that is a peculiarity.

So, you are asking for worst case recurrence rate data, assuming everybody who was not observed or left and went away recurred. I guess I am puzzled why you want that even though it can certainly be done.

DR. FISHER: If we go back to look at what we did at the last meeting, the question was -- and if we are going to think about using a surrogate marker -- in the people who are eradicated, what is the recurrence rate? So, that was our initial analysis that we were asking for. If you just took the people who were eradicated, what is the recurrence rate, including saying that the people who dropped out recurred and they were a failure.

DR. FREDD: My concern about coming to a conclusion based on individual studies to see if you can have proof of this surrogate, which had to be done through a meta-analysis of many studies, is what will you get from a conclusion based on small numbers within a particular study? In order to relate eradication rate as a surrogate -- maybe that is not a good word -- but as a surrogate for prevention of recurrence, that is based on a meta-analysis, a whole bunch of studies, to get up to an n where you can

see this phenomenon clearly.

When you are dealing with individual studies and individual treatment groups with evaluable cohorts and patients falling away as they go, since you have decided to treat at the active stage, we can certainly see the numbers, but we would have to interpret them very cautiously because of small cells.

DR. LAINE: By the way, I was not in any way trying to back away from the use of Hp as a surrogate. I was merely saying the way I would calculate recurrence, although I do not think we absolutely need it, is as I mentioned, not the way it was stated. I was not saying we do or do not need to do it.

DR. DUNN: The other problem to bring up is that you cannot get a true eradication in these studies because they were not designed that way. The people who were unhealed we do not know whether or not they were eradicated. So, it seems to me it is not appropriate to use the surrogate marker in these studies because we do not have it. That is true of this afternoon's studies as well.

DR. COMER: I would like to make another comment. I think that if we are going to use the surrogate marker in future studies, I do not think it is really fair to penalize these people, that we really do need to know

that, that we need to know maybe you have to wait a couple of weeks to determine it. You have to have a washout period from the treatment, but we do need to know by urea breath tests or by some modality whether the people who are unhealed are eradicated or not.

DR. FISHER: Dr. Temple?

DR. TEMPLE: Just the one last thing is that, fortunately, for everybody the healing rates are so high in the omeprazole cases, that the number of people for whom you do not have data is pretty modest. So, using a worst case in that case gives you a not-too-bad estimate of what the actual eradication rate is.

DR. COMER: No, but this is going to be a much bigger issue this afternoon.

DR. TEMPLE: Well, indeed. I was just talking about this case.

So, you can get eradication rates that are probably a little wrong because they are worst case, but they are probably not too far off because you are dealing with healing rates of 90-94 percent.

DR. FISHER: Let's go back then to what we are sort of asking Dr. Turney to do.

MS. TURNEY: Yes, please tell me what you want.

DR. FISHER: Because we are back to looking at

what we want in the recurrence at 6 months.

I would like to know -- I have to think about what I want to know now.

(Laughter.)

DR. LAINE: It is Hp positive, duodenal ulcer patients who healed. That is your denominator, and then the enumerator is how many at 6 months had recurrent ulcer.

DR. FISHER: Right. And if we do not know what their status is at 6 months as to the state of their ulcer, count them as a recurrence.

MS. TURNEY: Okay.

DR. FISHER: Dr. Bertino?

DR. BERTINO: I just would maybe direct a question to Dr. Dunn, which is we keep hearing about this outlier study. Just your thoughts about can a whole study be an outlier?

DR. DUNN: Well, I guess I would not have classified it that way, but certainly the reason we have p values is because we know it is a probability and not a given so that it is certainly possible for one study to be radically different from the others.

It probably has to do, though, with the patient population and whether or not we have the variables that allow us to distinguish the patient population in that

study from the others. We certainly have things like gender and age and so on, but those may not be the primary things that are causing the difference.

So, my guess is that what we have is a study whose patient population is in some way rather different from the other two.

DR. ELASHOFF: Not necessarily any less typical.

DR. MOLEDINA: Yes, and I had asked the company to look at those variables to see whether we can pinpoint, and they had looked at smoking and alcohol intake and certain other things. But they were similar in both the groups.

DR. FISHER: Distribution around the country was the same, length of prior ulcer history was the same as well?

DR. MOLEDINA: Same, yes. So, we just could not pinpoint anything.

DR. FISHER: Dr. Pizzuti, you looked like you were about to jump out of your -- no? Okay.

MS. TURNEY: I have a question for the company. Looking at my review, I cannot calculate those numbers directly from my tables. Do you have the database handy to calculate these numbers that the committee has requested?

DR. SIEPMAN: Yes.

MS. TURNEY: Okay, thank you.

DR. FISHER: Dr. Fredd?

DR. FREDD: Could I direct a question to the company as well as Dr. Moledina? Considering the healing of the acute ulcer, as I read the results, there was no statistical difference between omeprazole alone and omeprazole plus clari. Therefore, would you agree to conclude that there is no point in adding clari for acute healing in these Hp positive patients? Is that a reasonable conclusion?

You may want to add it at that point in order to eradicate to prevent recurrence, but that would be a maneuver of adding it in order to do something down the line, which is perfectly reasonable. But would there be a benefit? Have you shown a benefit over omeprazole alone for acute healing?

DR. MOLEDINA: No. We did not show that it was significant, but to get omeprazole definitely contributes. If you add omeprazole to clarithromycin, when you follow these patients and look for recurrence, definitely omeprazole plays a role. So, without healing, we cannot compute recurrence. We have to mention healing at some point.

DR. FREDD: I am not worried about mentioning it. I am trying to get at the claim, and the claim is the treatment of an active ulcer. The data that you have from the randomized cohorts of clari plus omeprazole versus omeprazole do not show a significant addition for whatever reason.

Does the company agree with that? There is a perfectly reasonable reason to start therapy to eradicate Hp at that point to prevent recurrence, but I am talking about a claim structure that includes the given of an added benefit in adding clari at this point.

DR. FISHER: Dr. Hunt, can you identify yourself?

DR. HUNT: Richart Hunt, Professor of Medicine and Gastroenterology, McMaster University, Canada. Perhaps I could comment, Dr. Fredd.

I believe that you know and members of this committee have heard from me on previous occasions various analyses that relate to duodenal ulcer healing and particularly the importance when dealing with acid suppression of both the degree of acid suppression and the duration of treatment.

Part of the reason in these particular studies I believe that you cannot detect the difference that you

have questioned is because the evaluable time point for ulcer healing is at 4 weeks. If you were to look at the 2-week time point, I believe that you would see a difference between an anti-secretory regime alone versus an anti-secretory regime with antimicrobial therapy. We have evidence in our own analyses from the total trial database that supports the treatment of the infection concurrently with acid suppression accelerating ulcer healing. In these studies, I think you will agree that there is a numerical superiority to the healing with the antimicrobial combination over the omeprazole alone.

DR. FISHER: But we do not have that data here.

DR. FREDD: Are you saying, Dr. Hunt, that there is a 2-week analysis we have not seen from these data?

DR. HUNT: No.

DR. FREDD: What are we going to see in terms of data?

DR. HUNT: I am saying not from these data. There are not. But what I am saying is that what you see here I believe is a numerical superiority but you cannot expect to see a significant difference at a 4-week time point because the healing rate of omeprazole alone, being as effective as it is --

DR. FREDD: Is so high.

DR. HUNT: -- is so high, yes.

DR. FREDD: Right. I understand.

DR. HUNT: So, your point I think is a well-taken point.

DR. FISHER: Dr. McQuaid?

DR. McQUAID: Just to follow up on this, there are data in omeprazole and amoxicillin that if you do not start the two concurrently, then your eradication rates fall. Are there any data like that with clarithromycin, that if you do not start them concurrently, if you were to treat with omeprazole first and then begin clarithromycin a few days down the line, then your eradication rates are any different? Does the company have any data on that?

DR. FISHER: Is there anybody from the sponsor who can respond to that?

DR. MOLEDINA: No.

DR. FISHER: No data.

DR. PERNET: I would just like to make a comment.

DR. FISHER: Can you identify yourself please?

DR. PERNET: Andre Pernet from Abbott.

I would like to make a comment to Dr. Fredd that acute healing of ulcer at the point, let's say

arbitrarily, of 4 weeks after the beginning of treatment is purely arbitrary, and it is not what counts for the patient. For the patient a long-term healing of the ulcer is what really counts. So, looking at the disease at 3 months, 6 months, or 1 year is really what counts for the patient.

DR. FISHER: I think that is what we are all sort of saying.

Dr. Temple?

DR. TEMPLE: Do you all believe these results are relevant to someone who healed his ulcer mistakenly, not including an antimicrobial regimen, say, 4 or 5 weeks ago? Do you have any view on whether you could justify a clari plus omeprazole regimen for someone who did not have an acute ulcer? Do you think these data are relevant to that? They had an acute ulcer, but it was a while ago and they did not know enough yet to include clari. Have they blown it forever? Do they have to recur before we can treat them? That is pertinent to labeling it would seem.

DR. PERNET: We did those studies the way we agreed with FDA to start with. These questions were not addressed.

DR. TEMPLE: Well, I was not criticizing the study. Is one to conclude that in the absence of an ulcer

you cannot eradicate? Is that a sensible conclusion?

DR. CRAFT: Dr. Craft from Abbott.

I think the real point is that since the two drugs have to work synergistically, that they are both necessary whether you treat an acute ulcer or you attempt to treat somebody who has a non-acute ulcer who had an ulcer in the past. You are still going to need the combination of the therapy.

DR. TEMPLE: Because you need to suppress the acid.

DR. CRAFT: Right.

DR. TEMPLE: But do you consider these conclusions applicable to someone who does not have an acute ulcer?

DR. CRAFT: Well, we did not do that in our studies, but we have treated patients with non-ulcer dyspepsia and H. pylori with these combinations and have had good results.

DR. FISHER: Dr. Fredd?

DR. FREDD: Could I just follow up on Dr. Temple's point? If you did a study in healed patients with your regimen and under a good numerator/denominator way of figuring out eradication, found eradication at the same rate that you found in the acute ulcer stage, would you

then be led to conclude that you have data that support the use of this in patients who have healed their ulcer but have an underlying ulcer diathesis? What I am asking for is a possible follow-up study.

DR. FISHER: Dr. Pizzuti?

DR. PIZZUTI: As Dr. Craft and Dr. Pernet mentioned, we did not specifically design a study to answer that question. To the extent that we are uncovering the relationship between H. pylori and subsequent ulcer disease, we may extrapolate the results and conclude what you said because most people that we treated were healed anyway, and maybe that is similar. However, we have to make that extrapolation to believe that or we do the study if you need to definitively prove it. But from what we know about H. pylori, I do not think it would be totally unreasonable to make that jump.

DR. FISHER: I think what we are going to do now, if there are no more questions direct to this point, is actually break and let people regather their thoughts and stretch their legs and come back. Let's try for 10 minutes.

(Recess.)

DR. FISHER: As people are getting back together, I would like to introduce the people around the

table who have joined us: Dr. Roselyn Rice from the CDC to my left on the anti-infectives group, and although they are not in their seats, Dr. Robert Temple, who has spoken, and Dr. Paula Botstein from the FDA as well who came in.

We are going to try I think to keep our questions a little bit more to the point and not go out. I am actually going to withdraw my request for the further calculation because the data I was looking for I think is not there in the study to be gotten. Because of the unhealed patients being dropped out of the study, we cannot really look at Hp status and healing rates. So, I am withdrawing my request for that analysis. The data will not be there and it will be too contrived to try to get anything out of it.

What we are also going to try to do, so we do not break up the second sponsor's presentation, is go on with the rest of this presentation and perhaps even break early for lunch at 11:30 and come back so we have the Glaxo Wellcome presentation all together instead of being broken up by lunch and still try to get out of here.

Can I ask Dr. Utrup?

DR. UTRUP: I am Dr. Linda Utrup, microbiology reviewing officer from the FDA, Division of Anti-infective Drug Products. I am going to be talking to you today about

the Abbott application obviously and the microbiology points that are involved with it.

The Abbott application has suggested the following breakpoints to be included in their package insert. For susceptible it would be less than or equal to 2; intermediate, 4; and resistant, greater than or equal to 8 micrograms per ml. Disk diffusion for susceptible, greater than or equal to 18; intermediate, 14 to 17; and resistant, less than or equal to 13. These are the breakpoints that are currently in the clarithromycin package insert at this time for other organisms for which there have been approved indications.

I am going to go ahead and go through some of the data.

The first is pharmacokinetic data. Abbott has done a good job of this this morning, so I will not belabor this, but just to show you quickly that this is the clarithromycin monotherapy. The red line here is the concentration in the plasma. The blue line is the concentration in the mucus; the yellow line, the concentration in the antrum; and the green, the concentration in the fundus. With a susceptible of less than or equal to 2 micrograms per ml, you can see that there should be ample clarithromycin here to take care of

the organism.

But we are using combination therapy, and as they stated this morning, the mucus concentration when you add omeprazole increases dramatically from 4 to almost 40 micrograms per gram. In the antrum that is also increased twofold, and the concentration in the fundus also has increased. So, an MIC of less than or equal to 2 micrograms per ml, you should have plenty of clarithromycin here to inhibit the organism.

The two U.S. studies used central laboratories for doing their culture and susceptibility testing and they were done by Dr. Graham's laboratory at Baylor in Houston, Texas. He used broth micro dilution MICs and disk diffusion techniques.

There were also two non-U.S. studies and they used agar dilution MICs and disk diffusion techniques.

I am going to focus on the two U.S. studies for the rest of my talk.

Biopsy specimens were taken and transported in glycerol-containing medium at minus 70 degrees C. They were cultured in brain heart infusion agar, to which 7 percent horse blood was added and also vancomycin, trimethoprim, nalidixic acid, amphotericin B to inhibit contaminating organisms. They were incubated at 37 degrees

C in 12 percent CO2 and 98 percent humidity, which is an appropriate microaerophilic environment to allow the H. pylori to grow.

Broth dilution MICs, as I said at the last advisory committee -- there is a lot of variation in the way susceptibility testing is done for H. pylori, and there are no standardized methods for doing susceptibility testing. So, I would like to go over what they used in this study.

They grew the organisms in brain heart infusion broth to which 10 percent horse serum was added and .25 percent yeast extract was added. The inoculum used as 5 times 10 to the 5th column-forming units per well. They incubated it at 37 degrees C and 12 percent CO2 for 3 to 5 days.

Disk diffusion was done on Mueller-Hinton agar to which 5 percent sheep blood was added. The inoculum was 10 to the 8th to 10 to the 9th column-forming units per ml. It was incubated at 37 degrees C for 3 to 5 days with the use of a CampyPak or CO2 enriched gas for the microaerophilic atmosphere, and a 15 microgram disk was used.

These are the overall results for the two U.S. studies. I have 104 patients here that I am considering in

the clarithromycin plus omeprazole arm, and of these, you can see that 98 percent were susceptible pretreatment. There were two isolates that were intermediate pretreatment and four that were resistant pretreatment.

H. pylori was eradicated from 72 of these 104 patients and all of these were susceptible pretreatment. Of these, there were 13 that had an ulcer recurrence.

All the numbers in these next two slides that are in parentheses will be the number that had ulcer recurrence.

H. pylori was positive in 26 patients here that had susceptible MICs pretreatment, and of that 26, 25 of them became resistant during therapy. So, 96 percent of the patients who failed on therapy became resistant during therapy. They started out as susceptible and became resistant.

There were isolates in 2 patients that were intermediate pretreatment that were resistant post treatment, both of which had recurring ulcer.

There were four isolates that were resistant pretreatment which remained resistant post treatment, 3 of which had a recurring ulcer.

So, 25 patients of the total or 25 percent became resistant on therapy, and of those that failed, 96

percent of them had organisms that acquired resistance.

The clarithromycin monotherapy arm here, I evaluated 77 patients. In both of these analyses, I included patients that had both pre and post-therapy MIC results that had a healed ulcer and -- had an ulcer, obviously, pretreatment and one that was healed at the end of therapy.

My numbers are different from the Abbott presentation in the last slide. They had 126 patients. I am evaluating 104. The difference here is that there were 9 patients that did not have post-treatment MIC results. So, they included those in their numbers and I eliminated them from my evaluation. Also, I think the rest of the difference between 104 and 126 were patients with unhealed ulcers which I did not include.

The total number that became resistant is the 31, as they had said, if you add those numbers up.

In the clarithromycin monotherapy arm, there were 74 patients that were susceptible pretreatment and 3 resistant pretreatment. Of these, 26 were H. pylori negative post treatment, 2 of which had a recurring ulcer. Of those that were H. pylori positive, there were 48 of these, and of that, 16 were susceptible post treatment, 1 was intermediate, and 31 were resistant.

So, this is approximately 40 percent of the population became resistant on clarithromycin monotherapy, and of those that failed, there were 65 percent that acquired resistance on clarithromycin monotherapy. Those that started resistant pretreatment remained resistant post treatment, all 3 of which had recurring ulcers.

So, to analyze the MIC values here, I plotted the number of patients versus the MICs on the x axis here. This is for clarithromycin and omeprazole treatment and these are pre-therapy MIC results. The large blue blocks here are the number of patients that would have, in this case, a pre-therapy MIC of .016 micrograms per ml. The gold triangles are those that became resistant on therapy. They started out as susceptible and became resistant. The red dots here are those patients that had H. pylori absent post treatment. The purple ones are those that had H. pylori present post treatment. You can see that most of the values are falling over here in this area of the graph at pretreatment and most of them are at a level of about .064 micrograms per ml or less.

In evaluating the post-treatment MIC values for the clarithromycin and omeprazole therapy, you see that most of the patients are over here at the value of greater than 8 micrograms per ml and there are a few here at 4

micrograms per ml. Again, the gold triangles are the ones that became resistant on therapy. The X here is the number of recurrences.

So, here we are comparing the clarithromycin and omeprazole pretreatment with the clarithromycin and omeprazole post treatment. You can see here that there really is definite bimodal population here with a bunch of patients with isolates here at .064 and less and the rest of them being over here at 4 or greater. The only isolates in between are these two right here, one at 25 micrograms per ml which became resistant on therapy and had a recurring ulcer and this one at 1 microgram per ml had the same thing, became resistant and had a recurring ulcer.

So, I am proposing that the breakpoints be put right here for susceptible, anything less than or equal to .064 as being susceptible, anything greater than or equal to 4 as being resistant.

The company has suggested that 4 micrograms per ml be included in the intermediate category, but I feel that it is more appropriate to be in the resistant category because that correlates better with the clinical outcome because all of those patients there at 4 had recurring ulcers and had H. pylori present post treatment.

The values in between, from .12 to 2 micrograms

per ml, I am suggesting might be in the intermediate range because there are only two isolates here and I think that we need more data before we can really decide whether they should be susceptible or resistant.

I would welcome any discussion about these breakpoints later.

We also looked at the clarithromycin MIC values, and again most of them here are in the susceptible range pretreatment. There were only three of the isolates here at the resistant range post treatment. Of the values, most of them were at greater than or equal to 8 or 4 micrograms here. This is the post-treatment response to the clarithromycin monotherapy.

So, in summary, I think that the appropriate MICs would be less than or equal to .06; intermediate, .12 to 2 micrograms; and resistant, greater than or equal to 4 micrograms per ml. I feel this has good bacteriological and clinical correlation with the MIC values.

I have not looked at any data on MBC values. They were not submitted to us.

The disk diffusion breakpoints that were proposed by the sponsor were susceptible, greater than or equal to 18; intermediate, 14 to 17; resistant, less than or equal to 13.

Here I have plotted for the clarithromycin and omeprazole arm the number of pretreatment isolates here versus the zone diameter. The gold bars here represent those MICs that were resistant at the value that I had set, the greater than 4 micrograms per ml. These two fuchsia bars are the ones that are included in the MICs that I set as intermediate, and the blue bars here are the ones that have values of less than or equal to .064 micrograms per ml.

As you can readily see, there is a very large range of zone sizes here for the disk diffusion results. At this time I think it would be appropriate to wait to see if we can get other variations on the testing parameters, namely, the disk content or the media selection or whatever, to get these zone sizes more in range with what is normally accepted.

So, what I had envisioned here is that we accept these breakpoints as susceptible, less than 0.06; intermediate, .12 to 2; and resistant, greater than or equal to 4. Included into the package insert, what I am thinking of doing is having a separate section in the clarithromycin package insert for susceptibility testing of Helicobacter pylori similar to the one that is already there for Mycobacteria. I will clearly state that there

are no approved susceptibility testing methodologies, but if you use the methods that were used here, with Dr. Graham's permission, of course, one would be able to be reasonably sure that you could have good correlation I think between the clinical and bacteriological results and the MIC values here.

I do think it is important that we establish breakpoints for Helicobacter pylori because, as I had pointed out, there is quite a bit of resistance that does develop on therapy and it would be useful to be able to have this information.

Thank you.

(Applause.)

DR. FISHER: Questions for Dr. Utrup? Dr. Laine, then Dr. Craig?

DR. LAINE: You had a somewhat higher resistance level than Abbott reported, but you looked like you only included people who had ulcer recurrence. Is that the difference? You said ulcer recurrence, Hp positive. What about the patients who did not have ulcer recurrence but remained Hp positive?

DR. UTRUP: Those were only patients that were Hp positive. The ulcer recurrence was a subset of those. I do not break it out.

DR. LAINE: So, that 26 was people who were ulcer positive and ulcer negative.

DR. UTRUP: Those 26 were patients that were Hp positive post therapy.

DR. LAINE: Whether they had ulcer recurrence or not.

DR. UTRUP: Right.

DR. LAINE: So, the ulcer recurrence was not related referring to that overall group on your slide.

DR. UTRUP: No. Well, actually it was. There was an X on there that did show that. Are you talking post therapy, the clarithromycin and omeprazole?

DR. LAINE: I was just wondering why your resistance calculation was so much higher. They are both high, but yours was higher than theirs. I was wondering what the difference was. 96 percent versus whatever theirs was, two-thirds.

DR. UTRUP: I would guess that the answer might be that they did it per the 126 patients. Is that correct? And I evaluated 104 patients, the difference being that I did not include patients that did not have post-therapy MICs. I mean, I included those that only had pre and post-therapy MICs. They included those that had pre-therapy MICs and did not include those that were Hp positive but

did not have post-therapy MICs.

DR. CRAIG: Am I right, in looking at the clarithromycin alone and then the combination, that it looked like the number of people that developed resistant organisms was relatively the same? The difference between the two is that you did not have failures with susceptible strains in the group that got the combination.

DR. UTRUP: Yes, that is correct.

DR. CRAIG: And if you total up the number that started off as resistant, how many was that and what was the overall response in that group?

DR. UTRUP: Could I have the projector back on? The slide shows it quite well.

DR. CRAIG: So, 3 out of 4. If you added the intermediates, you have 5 out of 7 recurred then.

DR. UTRUP: Correct.

DR. FISHER: Dr. Pizzuti?

DR. PIZZUTI: As I mentioned during the presentation, the original breakpoints that Dr. Utrup used were the default breakpoints for all the indications for clarithromycin, and what we would like to do, at your indulgence, is to present the full data that we have collected since filing the NDA on all the isolates that we have, including non-U.S. isolates. So, there will be some

additional information. Dr. Tanaka has just a few slides that can summarize that before you make any conclusions regarding that.

DR. FISHER: If it is just a couple slides.

Dr. Bertino, do you want to ask a question? Wait for that, okay.

DR. FISHER: Dr. Tanaka?

DR. TANAKA: Ken Tanaka, Abbott Laboratories.

As we saw with Dr. Utrup's analysis -- and I basically have our rendition of that analysis on this slide -- clearly H. pylori under standard testing, in this case, supplemented brain heart infusion broth by microtiter testing, clearly separates into two distinct populations, one that we could call susceptible and one that we would call resistant, with a very large gap with very few examples in that gap separating the two populations. Based on this analysis, then the susceptible population would have an MIC range of 0.004 micrograms per ml to 0.06, and the resistant, 4 to 8 micrograms per ml.

What we have done more recently is to look at a variety of testing methodologies, but let me begin first with our overall picture from the clinical trials, both the U.S. and Europe. This involves a combining basically of data generated from two different methodologies, one the

microtiter of Dr. Graham's laboratory and the other the agar dilution method in Dr. Ghoneim's laboratory.

When we look at this data, again it is clear that the U.S. isolates again are here. Now we see the European isolates come into play both here and out here. What we see is that in fact, depending on your methodology, the populations shift in MIC range, although their relative relationship really does not change.

Based on this, then we would say that in fact our susceptible population would split up probably at 0.5 micrograms per ml and the resistant population we would want to reduce to 2 micrograms per ml.

So, part of the ongoing studies that we have in collaboration with Dr. Graham is to evaluate additional methodologies and see how everything compares. In the blue we have the micro broth dilution test using supplemented BHI. In yellow we have the E-test, and in red the agar dilution test using Mueller-Hinton agar supplemented with horse blood but pH adjusted to pH 8. In fact, these three methodologies basically give the same overall picture, two populations widely separated. However, the micro broth dilution test tends to read or give a range slightly lower, perhaps a tube lower, than especially the agar dilution method at pH 8.

We have taken this one step further and evaluated agar dilution using Mueller-Hinton agar unadjusted for pH but supplemented with horse blood. We have done this because Mueller-Hinton is the preferred media for susceptibility testing. We have found that it supports the growth of H. pylori primary isolates very well when supplemented with horse blood and that pH adjustment from an operational standpoint from the clinical laboratory is probably undesirable and might affect standardization of other testing. So, we are trying to get away from the pH adjustment.

When we look at this, then what we see is that the MIC range of the unadjusted Mueller-Hinton now goes up to 0.25 micrograms per ml and a corresponding shift in the resistant population. So, again it is clear that the populations, widely separated, simply shift around depending on your methodology.

Further, we can say that the breakpoints that we might want to consider would continue to perform within the parameters of almost all the tests that we have.

So, in conclusion, we would ask the advisory committee to consider breakpoints of susceptible, less than or equal to 0.5 micrograms per ml, intermediate at 1 microgram per ml, and resistant at greater than or equal to

2 micrograms per ml primarily based on using Mueller-Hinton agar supplemented with horse blood but can be applied to broth micro dilution testing and E-testing as well.

We would also ask the subcommittee to consider the use of disk diffusion because, as you saw from Dr. Utrup's presentation and our analysis would indicate, the susceptible population can be distinguished quite readily, just as in the MIC testing, using a susceptible breakpoint of greater than or equal to 26 millimeters; intermediate, 19 to 25; and resistant, less than or equal to 18 millimeters.

Thank you.

DR. FISHER: Questions from the committee for Dr. Tanaka? Dr. Reller?

DR. RELLER: What is again the pH of the micro broth dilution?

DR. TANAKA: We have not determined that. I think brain heart infusion on normal reconstitution runs about 5 to 7-8, in that range. I think it is a little bit higher than standard Mueller-Hinton. We are also in 12 percent CO2 and the buffering capacities of the two media may be different.

DR. RELLER: So, there was no control for that.

DR. TANAKA: As far as?

DR. RELLER: The micro broth dilution. We do not know what the pH is for sure and we do not know from the different centers in Europe and the U.S. --

DR. TANAKA: No, we do not. That is right. We have no idea of lot-to-lot variations, et cetera.

DR. FISHER: Dr. Megraud?

DR. MEGRAUD: I think you cannot determine the breakpoints in this way. I think it is important to correlate the clinical success with the MIC of the strain and probably you have too few strains, especially in the intermediary position, to conclude. I do not think that your demonstration changed a lot to what Dr. Utrup proposed before.

DR. TANAKA: No. It in fact basically Dr. Utrup's proposal except that things have shifted depending on your testing procedure. Relationships do not change. The resistant population is still there.

DR. MEGRAUD: The value that you propose for susceptibility is much different, is quite different.

DR. TANAKA: Yes.

DR. MEGRAUD: So, I am not sure if you are right.

DR. TANAKA: No. Again, as you say, there are very few in that intermediate category.

DR. MEGRAUD: Another way would be to compare the concentration of clarithromycin you are able to reach in the tissue in the human situation to the MIC of the strains. So, do you have such data?

DR. TANAKA: Dr. Pizzuti presented the gastric mucosal levels, which in the mucus layers up to 30 micrograms per gram -- 40 micrograms per gram, and in the antrum tissue it was 10 to 20 micrograms per gram. So, well above the MICs, you could argue, even of the resistant organisms.

DR. MEGRAUD: Yes, but this is in the mucosa. What about the mucus?

DR. TANAKA: In the mucus it was 40.

DR. FISHER: It was 40 in the mucus.

Dr. Bertino?

DR. BERTINO: I would like to expand on that question because trying to correlate the kinetics and dynamics of clarithro, you are well above the MICs even in mucus where it was 39. Then we have not even talked about 4-hydroxy clarithro which appears to have very good antimicrobial activity, at least according to the data that we were given. Based on just the clearance of these agents, you should be above the MIC for the whole dosing interval for both of those compounds, clarithro and

4-hydroxy. So, I am not sure that if you have an organism with an MIC of greater than .064 -- let's say 1.25 -- why that would be considered resistant based on the concentrations that you get in the antrum and the fundus and the mucus layers with a combination of clarithro and omeprazole. You are well above the MICs for the whole dosing interval.

DR. UTRUP: Primarily it is because of the lack of clinical correlation with those organisms that are in the resistant range.

DR. BERTINO: You are kind of using this as a surrogate for sensitive, intermediate, and resistant. I wonder then if there is any relationship to the MICs based on the kinetics of these agents at the site of infection.

DR. CRAIG: Yes, Frank?

DR. JUDSON: I think whether it is .06 or .5, I agree we are being highly conservative.

But what bothers me is that we have somehow managed to shift the curve by maybe tenfold. Abbott does not at this point know whether that is even due to pH which has not been measured, and one would think that the susceptibility testing would be highly sensitive to pH. So, I do think that whatever is chosen, we have got to be able to standardize the MIC technique so that we are not

dealing with unexplainable 10 to 15-fold differences.

DR. CRAIG: Yes. Let me just comment in reference to the mucus levels. Again, what we do not know is whether there is binding of the drug to mucus so that the free concentrations may be significantly less. So, I think it is hard to just use the values that are reported and come up with an actual antimicrobial effective concentration. So, it may be significantly less because of protein binding or something like that.

DR. FISHER: Dr. Rice?

DR. RICE: Hi, Roselyn Rice.

One follow-up question to Dr. Craig and Dr. Judson. Does Abbott have data inter-laboratory reproducibility for the data they presented?

The second question is on MBC. Are there MBC data available?

DR. TANAKA: We have no data on inter-laboratory variability.

MBC data is available in the literature and it is quite bactericidal.

DR. FISHER: Dr. Utrup?

DR. UTRUP: I would just like to make a comment that this is the first time I have seen the Abbott data that they have presented. It was not submitted to the

submission. So, I cannot really comment on it.

DR. FISHER: Dr. Elashoff?

DR. ELASHOFF: Apropos of the issue of the observed MIC, that was only the mean. It did not give a standard deviation, so you could easily have some people that are well away from what was shown there.

DR. FISHER: Dr. Norden?

DR. NORDEN: Well, as a newcomer, I would just like to comment. I do not think I would be prepared to try to set susceptibility criteria at this point. I think the data from Abbott which was just presented is very quick, and I think that I am not convinced that the methodologies all give extremely similar results. I would really like to look at that more closely and certainly have someone who is more of an expert microbiologist look at it. I think it is an important decision and those are huge differences, as Frank points out.

DR. FISHER: Other questions from the committee? Dr. Reller?

DR. RELLER: One thing seems clear to me that if one were to set breakpoints, one certainly cannot set breakpoints based on a combination of a multiplicity of methods, some of which do not have essential parameters delineated, specifically pH with a compound that is known

to be extraordinarily sensitive to changes in pH.

Given that, the whole art and science of susceptibility testing with H. pylori and the stringency required for a reproducible test that correlates highly with clinical outcome or recurrence of disease perhaps in this situation, what one wants is not trying to simulate necessarily what is going on at the mucus layer but something that is predictive of the outcome that one wants with a test that is defined in every parameter, ideally one that is amenable to doing with current technology available, current media, et cetera, and to work all those things out. Basically this area is in its infancy. I think it is way premature to get locked into the breakpoints.

In the meantime, to give some operational viewpoint it seems to me the most conservative breakpoints with the widest intermediate range is the most sensible first pass with a specified -- and it may be a literature reference -- methodology until such time as a consensus group like the NCCLS, in collaboration with the FDA, can come up with a perhaps more practical method for susceptibility testing where one could do it by different methods, including instrumentation, E-test, disk diffusion, broth dilution by microtiter methodology, and then get

these endpoints more precisely defined.

So, I would simply urge that if we make a recommendation for breakpoints, that they be with a broad intermediate along the lines that are presented by Dr. Utrup with one methodology specified, but we cannot have a multiplicity of methodologies applying the same breakpoint.

DR. FISHER: If there are no other comments or questions of the sponsor from anybody else in the group, I do not think we are waiting for any other data analysis at this time. Is that correct, Dr. Craig?

DR. CRAIG: That is correct.

DR. FISHER: There is agreement there.

Why don't we go on to the questions that have been raised for the committees?

Let me just clarify who is voting and who is not voting, but we would like opinions I think, as we did last time, from our consultants and guests. The people who are voting, going around the table -- I will start on my left -- are Dr. Elashoff, Dr. Banks-Bright, Dr. Rice, Dr. Judson is a voting consultant, Dr. Butt, Dr. Dunn, Dr. Comer, Dr. Craig, myself, Dr. Kirschner, Dr. Norden, Dr. Reller is a voting consultant. Dr. Dunn was a voting consultant. And the non-voting consultants then are Dr. Walsh, Dr. McQuaid, Dr. Laine, and Dr. Megraud. Correct?

DR. CRAIG: That is correct.

DR. FISHER: What I am going to do is read through the introductory comments that are here and then we will go around.

Omeprazole is currently indicated in the United States for short-term treatment of active duodenal ulcer, short-term treatment of symptomatic gastroesophageal reflux disease poorly responsive to customary medical treatment, short-term treatment of erosive esophagitis diagnosed by endoscopy, maintenance of healing of erosive esophagitis, and long-term treatment of pathological hypersecretory conditions.

Clarithromycin is currently indicated in the U.S. for pharyngitis/tonsillitis due to Strep. pyogenes; acute maxillary sinusitis due to H. influenza, Moraxella catarrhalis, Streptococcus pneumoniae; acute bacterial exacerbations of chronic bronchitis due to H. influenzae, M. catarrhalis, or Strep. pneumoniae; pneumonia due to Mycoplasma pneumonia or Strep. pneumoniae; uncomplicated skin and skin structure infections due to Staph. aureus or Strep. pyogenes; treatment of disseminated Mycobacterium avium and Mycobacterium intracellulare; acute otitis media due to H. influenzae, M. catarrhalis, or S. pneumoniae; prevention of disseminated MAC disease in patients with

advanced HIV infection.

The sponsor conducted four multicenter controlled clinical studies, two domestic and two foreign, in H. pylori infected patients with active duodenal ulcers. Three of these studies, two domestic and one foreign, were designed to demonstrate that the combination of omeprazole 40 milligrams daily for 2 weeks plus clari 500 milligrams t.i.d. for 2 weeks, followed by omeprazole 20 milligrams q.d. for 2 weeks is safe and effective in H. pylori infected patients with active duodenal ulcers.

In addition, the clinical studies were designed to demonstrate that each component of the regimen makes a contribution to the claimed effect.

The sponsor currently seeks the following additional indication for their drug, clarithromycin, when given in combination with omeprazole: "treatment of active duodenal ulcer and prevention of duodenal ulcer recurrence associated with H. pylori infection."

After all of that, to the questions. One, do these clinical trials demonstrate the safety and effectiveness of the combined regimen, clari plus omeprazole, in patients with active duodenal ulcers?

Dr. Kirschner?

DR. KIRSCHNER: I guess I have some problem

with the way the question is stated "for active duodenal ulcer" because the one place where it did not show to be statistically different was in ulcer healing. I do not have any problem with H. pylori eradication. So, I do not know quite how to answer this question. It is too broad for me.

DR. FISHER: Would you say yes then, but "For example: i) H. pylori eradication" -- if yes, for what indicators should the product be labeled? Let me read it that way. Let's start again.

If you say yes, for which indication should the product be labeled: for H. pylori eradication to reduce the risk of duodenal ulcer recurrence, or for overall success? If overall success is used as the efficacy endpoint, how should it be defined? Ulcer healing and no ulcer recurrence, ulcer healing and H. pylori eradication, ulcer healing, Hp eradication, and no ulcer recurrence?

And if no, what additional studies/data are needed?

DR. MOLEDINA: Dr. Fisher, let me make one thing clear. We have put that question that way because the studies were designed that way. All the patients in our studies were patients with active duodenal ulcer, and that is why that question is written the way it is written.

DR. KIRSCHNER: I think it clearly shows that it is successful for H. pylori eradication, the combination as opposed to the single components individually.

With regard to recurrence and prevalence of ulcer at 6 months, that is less clear for me. I think that just based on the studies that have been presented to us, without knowing any other additional information, I have trouble accepting that one of the major U.S. studies is an outlier that shows very different results from the other ones. So, it is very difficult for me to say other than H. pylori eradication at this point, although my bias is that it probably does have a greater effect than what we are stating, but I cannot say it on the basis of the information that is presented to me.

DR. FISHER: Dr. Laine, a question?

DR. LAINE: Is it reasonable, if we accept H. pylori eradication for this and any other regimen that comes up, to actually define a statement about what H. pylori eradication means? We did that at that last kind of consensus conference, if one labels something for H. pylori eradication to actually have a statement about what that means.

DR. FISHER: Percentages?

DR. LAINE: No, not percentages, but that means

that it is a surrogate for prevention of --

DR. FISHER: Well, it is stated in there, "to reduce the risk of duodenal ulcer recurrence."

DR. LAINE: Right. And should we do that with any ulcer just to do that?

And the other point is the idea of active versus all ulcer disease, and do you want to revisit that as well or not?

DR. FISHER: Well, I do not think we can revisit the idea of non-active ulcer disease, as Dr. Moledina said, since the studies that are presented to us here today deal just with active ulcer disease.

So, Dr. Dunn?

DR. DUNN: I agree with that but I think it goes even further. The studies presented to us today do not allow us to vote on eradication. We know eradication only in healed patients.

DR. FISHER: That is one of the reasons, remember, when I was asking for my other data on looking at eradication and rates of recurrence in that the people who were unhealed at the end of the initial 4 weeks of therapy, we do not have Hp status on and they were dropped, and we do not have any data on whether they recurred, if they healed, or whatever. So, we are down to only half of that

group in the patients who healed.

DR. LAINE: The difference, though, between those evaluable at post treatment and those evaluable at 4 to 6 weeks was only about I think 3 or 4 in each group.

DR. COMER: Yes, it is very few patients.

DR. LAINE: So, it is about 61 versus 64 or that kind of thing.

DR. CRAIG: The percentage failure in terms of healing I think 12 percent was the most, but in one of the studies it was even as high as 99 percent success. So, even if you add those in and say that they were not eradicated, I think the data still would support that the compound does eradicate the organism.

DR. FISHER: Dr. Norden?

DR. NORDEN: I am not sure where I am at this point and that is either because I was not here in October -- it is either a plus or a minus.

(Laughter.)

DR. NORDEN: I think I am going to make a quick statement and then I would say a vote.

But I think that you can eradicate this organism in a certain percentage of patients, and I do not really know what percentage demonstrates effectiveness or not until you see more trials done in basically the same

way with different agents and then you can achieve a comparative efficacy. Is 60 some odd percent in the U.S. studies effectiveness or not?

Then the second issue, which I am still very concerned about, is resistance which develops in a large number of patients who fail and that has both implications for the patients and ecologic implications.

If pressed, I would say yes, I would vote that the combination eradicates H. pylori, and I am not as convinced about the rest of the data for reducing the risk of duodenal ulcer recurrence.

DR. FISHER: Dr. Bertino?

DR. BERTINO: I was here in October and I am just as confused.

(Laughter.)

DR. BERTINO: I think the data that I saw was that you do get eradication with the combination greater than with omeprazole alone, for example. But I think I have some of the same concerns Dr. Norden discussed, particularly in the area of resistance.

So, I guess I would say yes, and I guess H. pylori eradication would be -- I think I feel comfortable with that, but I do think there are more studies that need to be done in the area.

DR. FISHER: Dr. Reller?

DR. RELLER: We are voting on proposed indication labeling, and I vote yes word for word for the bold print indication, "treatment of active duodenal ulcer and prevention of duodenal ulcer recurrence associated with H. pylori infection." I think it is a splendid, succinct statement about what this combination -- the data we have seen -- does, that each component adds something. If you take one out, you have something less in one or the other aspects of this.

And the issues of resistance and what they are caused by I think we have got some pretty good indicators that if you use the combination, virtually all the failures are owing to resistant organisms that are left. If you use the antimicrobial alone, most of them are owing to that, but there may be some component of subtherapeutic concentrations of drug, and how to avoid the resistance, how to improve the overall success rate from the 50-60, thereabouts, percentage are the sorts of studies and future trials that we would like to see against this comparator combination, as Dr. Norden has pointed out.

So, I think it is very complicated and it can be confusing, but we can make it more confusing than it really is. This combination is effective, not as effective

as we would hope in subsequent generations of products perhaps, but it is effective I think in the data presented for the treatment for active duodenal ulcer and prevention of duodenal ulcer recurrence associated with H. pylori infection. And I would vote precisely for that with an unqualified yes and look to future studies.

DR. FISHER: Dr. Walsh?

DR. WALSH: I guess we all look at things from the other perspective being in GI or infectious disease.

I think it is quite clear from tables 7 and 15 that using the real worst case analysis, this combination is highly effective for eradication of Hp. I certainly would not want to have an indication that did not mention eradication of H. pylori. Ulcer-free and Hp negative in the short term are so closely interrelated, it is hard to pick out. Even using the worst case kind of analysis at 6 months, it appears that you have a reasonable indication for long-term prevention, which is really, it seems to me, the goal of Hp eradication.

So, I have more trouble with the "treatment of active duodenal ulcer" part. I think the data are sort of soft. In one of the studies, it is not superior to omeprazole alone and in the other one it is.

So, I would be, in order of strength, most

positive on eradication of H. pylori, second for the prevention of recurrent ulcer, and third, equivocal on the on the treatment of acute ulcer.

DR. FISHER: Dr. Comer?

DR. COMER: I have a question. In this indication, as long as it is equivalent to omeprazole alone, do we really have to show superiority given that the goal is that it does treat the ulcer, it does eradicate the organism, and in those that we have eradicated, the recurrence is reduced? It seems to me that you do not need to show that it is better than omeprazole. It is really pretty hard to be better than omeprazole. I do not know that that is necessary to approve this combination for the treatment of acute duodenal ulcer.

DR. FISHER: Dr. Fanning, Temple, or Fredd or Dr. Botstein? Or Dr. Feigal has not said anything yet today. Thank you.

DR. FEIGAL: Let me take a crack at the spirit of the combination regulations which actually are written to apply to fixed combinations, but I think the same spirit is being applied here.

The notion of the approval of a combination, as the committee is aware, is that you want to have some idea of what each component does and that each component adds

something to the combination. They do not have to add the same thing. In fact, the regs explicitly describe the case where one component may in fact make a second component safer, as an example, where the overall efficacy would not be better, but the combination is safer than the drugs alone.

So, I think in this case there are a couple of ways that you can approach this when you look at the description of the indication. Since the trials were used to describe the treatment in a given setting, that setting is the one that you have probably the most comfort about recommending the use of the drug. So, acute ulcer comes into the picture in those terms.

But then there is also the broader issue in terms of what does it mean to treat ulcer disease in 1995 or soon 1996. If that includes not only the aspects of healing, but it may also include aspects of treating H. pylori in patients whose ulcer disease is due to H. pylori. So, that is a broader concept of what the role of each component is, but there is not a requirement that each component adds something to the primary role of the other component.

DR. FISHER: Dr. Temple?

DR. TEMPLE: Just to follow that thought.

There may be a role for both. In fact, everybody obviously thinks there is. But to say that clari helps treat the ulcer would not correspond with any data that are here. There are some suggestions that that might be true if you had a more resistant population or something, but that literally has not been shown. So, the contribution is, as David said, in getting rid of the organism, not necessarily in healing the ulcer.

DR. FISHER: Dr. Fredd? Short.

DR. FREDD: Just very short. Is the question whether you want to indicate this for treatment at the active ulcer stage or for a treatment that in a combination way benefits the acute healing of the ulcer? It seems to me that maybe some of the discussion is treatment of acute ulcer patients but not necessarily conveying the notion that the combo is better than the single component at the active ulcer healing if that is complex language.

In other words, the patient population to be treated is patients with acute ulcers. It does not necessarily mean that the combo is better than the individual component, omeprazole, in terms of the active ulcer healing, but rather when you use them in combo, you get this additional benefit of eradication which leads to prevention of recurrence.

DR. FISHER: I think what you can say is what Dr. Reller was saying. The bold is -- almost to reword it -- in the treatment of reducing the risk of duodenal ulcer recurrence associated with H. pylori -- sorry -- reducing the risk of recurrence of duodenal ulcer in patients with active duodenal ulcer associated with H. pylori infection. If you redid the arrangement, it would make the question of the treatment of active duodenal ulcer disease disappear as opposed to thinking that you needed both components as opposed to one, that this is a thing that is used in combination and is looking at the outcome.

So, taking the "treatment of active duodenal ulcer" out of that first part and putting it more for reducing the risk of recurrence in those patients with active duodenal ulcer associated with Hp would be the appropriate way to make the indication.

DR. LAINE: Shouldn't we say it is treatment of patients with active duodenal ulcer, which is really what was studied? So, just by putting "patients with active duodenal," you are accomplishing the same thing I think.

DR. FISHER: Say that again.

DR. LAINE: Treatment of patients with active duodenal ulcer disease is what you are doing. You are not treating the active duodenal ulcer disease. You are

treating patients with. So, by putting those two words in, you might overcome the concerns. Patients with duodenal ulcer disease and H. pylori infection, obviously.

DR. FISHER: Right. Okay.

Dr. Reller, you look like you are --

DR. RELLER: We all understand what the strengths and the limitations of the data are. We were presented four studies in which this combination was used, and the data are there, that if one eliminated one or the other components of it, by the design of the trial, one would end up at 6 months or at a year in a couple of the studies with the result that would be less than if you did not have both components.

So, one has a study design and results, and the results support the conclusions that are in this statement. To try to hedge on all the other issues, et cetera -- it may be true, but let's have the other studies. These studies were designed in a certain way and I think that this statement could be a reasonable conclusion scientifically from the data presented.

It has nothing to do with whether at 2 weeks one actually needs the clarithromycin there or does not need the clarithromycin there. The question is when you use it as it was given in these studies, did it have the

end result at 6 months consistent with the labeling, and I think that it does.

DR. LAINE: I thought the distinction just was whether it really is necessary to heal the ulcer, and by saying treatment of the active ulcer, you are saying it heals the ulcer. So, I think that was the point that was being made, that if you say treatment of a patient with an active ulcer, that would be a distinction.

DR. RELLER: Looking at the issue of what is the indication, the studies were by definition for patients who at the time this therapy was initiated had an active ulcer.

DR. LAINE: Right. So, that is treatment of patients with active duodenal ulcer disease, but it does not mean that the treatment actually hastens the healing of the active ulcer itself.

DR. FISHER: Because we do not actually have data from those patients who did not heal -- the ulcer did not heal -- were dropped out and we do not know what happened to them.

DR. RELLER: This is an ellipsis. Obviously you are treating patients. You are not treating dogs, cats, test tubes or anything else.

Given a patient -- one has a patient -- this

drug or combination of drugs is indicated for the treatment of active duodenal ulcer and prevention of duodenal ulcer recurrence associated with H. pylori infection in that patient or in patients with. I mean, come on. This is an attempt to have a succinct statement about what you are going to use this drug for when a physician is presented with a patient who has this entity.

DR. FISHER: Dr. Kirschner?

DR. KIRSCHNER: I just wish I could see things that clearly. I agree with you. We all care about what the long-term effect for the patient is. That is why we are here.

But the prevalence at 6 months in one of the pivotal studies was 52 percent and it was 50 percent in one of the clarithromycin-alone. So, one of their major studies essentially shows no difference in prevalence at 6 months. This is the one they are labeling an outlier, and I just have problems saying that it is very clear-cut that the evidence is so one-sided.

DR. RELLER: That is why the FDA requires more than one study.

DR. FISHER: I would rather go around the table before we have the sponsor make a comment. People on the other side of the table are getting anxious.

VOICE: (Inaudible.)

DR. FISHER: I am sorry?

VOICE: Everybody is going to forget what was said.

DR. FISHER: Okay, let's clarify the statement and make it brief please.

DR. PERNET: I think the issue here is not the true combination therapy between drug A and drug B, both approved for the same treatment for the same disease. We have omeprazole approved for the treatment of duodenal ulcers and we are trying to see if adding clarithromycin will benefit the patient. So, what we just have to prove is added benefit when adding clarithromycin to omeprazole, and that was clearly shown in all studies statistically significant.

So, from an approval point of view of what will really benefit the patient, I think those studies are valid because no one in this room will want to treat an active duodenal ulcer with just an antibiotic.

DR. FISHER: Dr. McQuaid?

DR. McQUAID: I think I agree with Dr. Reller and Dr. Walsh more or less. I think it clearly has been shown to eradicate Hp. I think there are better regimens out there, and I think it unrealistic to think that by

approving this regimen that this is what will be used by people because this is not, I think compared to other trials that are out there, probably the best regimen. But it works and it seems to be an effective regimen.

In terms of its impact upon ulcer recurrence, I am concerned with the one study that is discrepant with the other three studies submitted here as well as multiple other trials, but I think the RBC data this afternoon also shows that the recurrence rates in Hp-eradicated people may be higher than we were led to believe before. I think that is disturbing.

Nevertheless, I think that the studies here do support that by eradicating Hp, we do decrease ulcer recurrence. Whether it is a 95 percent reduction or whether it is a 70 percent reduction I guess remains to be seen.

So, I would support the statement more or less as written I think of treatment of patients with active duodenal ulcer and for the prevention of ulcer recurrence associated with H. pylori infection.

DR. FISHER: Dr. Laine?

DR. LAINE: I basically agree. I would just again say something like treatment of H. pylori infected patients with active duodenal ulcer disease, something

along those lines. But I agree with most of what has been said.

DR. FISHER: Dr. Megraud?

DR. MEGRAUD: My general opinion. First, I think that clarithromycin is the best antibiotic to treat H. pylori.

Second, I think that the studies that were conducted by Abbott were very well designed and especially on the point of your diagnosis.

Further, I was surprised to hear that clarithromycin does better than omeprazole for symptom relief.

(Laughter.)

DR. MEGRAUD: But I am worried on the problem of resistance of H. pylori to clarithromycin. If you consider the intention-to-treat analysis, the rate of success is about 54 percent. We saw that a lot of those patients not eradicated developed resistance against H. pylori. So, in contrast to what was said, there is a problem I think to treat these patients after with clarithromycin.

Especially I do not agree with the statement which was made that there is a reversion of resistance because we have data showing clearly that is not true, it

is not possible.

DR. FISHER: Dr. Elashoff?

DR. ELASHOFF: From a statistical point of view, I think it is clear that the combination does eradicate Hp better than either one alone. Also, this B definition of success, if we look at those who were healed and have Hp eradicated, that has essentially the same sort of thing.

It is less clear to me to what extent one can really conclude that this is the best way to reduce recurrence, especially since in those who become resistant, you may have more trouble in the future than you did in the past because you have sort of changed the Hp with which they are infected.

So, it seems to me for eradication or for this B definition of overall success, it is clear. I am less clear about making a claim about reducing ulcer recurrence.

DR. FISHER: Dr. Banks-Bright?

DR. BANKS-BRIGHT: I am inclined to agree with Dr. Reller that I think we have seem some well-designed studies with respect to this, and that I would say yes, that these trials have demonstrated the safety and effectiveness of a combination of clarithromycin and omeprazole in patients with active duodenal ulcers.

What I have had some problem with this morning -- and I guess after Dr. Reller made his last comment, I have been trying to pick apart each little aspect of this and find that I, yes, have some problem with resistance as an issue. I was asking Dr. Elashoff about sample size and so forth. I think we do need more studies, but after picking it apart, as I have done this morning, I still come back to an answer of yes. I do think that the combination is effective.

DR. FISHER: Dr. Rice?

Let me just ask Dr. Fanning. You are getting a whole bunch of different, as opposed to clear yes/noes, comments around here.

DR. BANKS-BRIGHT: Mine is a yes.

DR. FISHER: After we all finish, if there are any additional questions you want to ask from your side, please feel free to be thinking about them.

Dr. Rice?

DR. RICE: I am going to have to give you again a qualified yes to the question of safety and efficacy. I agree with the yes with respect to H. pylori eradication. I still have trouble with the question of qualifying overall success based on again the data presented today, regardless of what is in the literature.

I would like to advocate with that response, which only I am sure confuses the issue more, more extended follow-up to assess the persistence question of resistance and recurrence of ulcer disease. That is my comment.

DR. FISHER: Dr. Judson?

DR. JUDSON: Yes.

(Laughter.)

DR. FISHER: Now that I have gotten up from fainting, yes to what? If yes, to which one then? You have to pick something.

DR. JUDSON: Yes to your question. Do these clinical trials demonstrate the safety and effectiveness of the combined regimen in patients with active duodenal ulcers? And yes, should the sponsor receive an indication for clarithromycin which reads, "treatment of active duodenal ulcer and prevention of duodenal ulcer recurrence associated with H. pylori infection."

DR. FISHER: Okay.

Dr. Butt.

DR. BUTT: Ditto.

(Laughter.)

DR. FISHER: Dr. Dunn.

DR. DUNN: Make that three.

DR. FISHER: Dr. Comer.

DR. COMER: Make it four.

DR. FISHER: Dr. Craig.

DR. CRAIG: I would say yes, but again I would change that sentence a little. Instead of where it says "and prevention," I would change that to "to prevent duodenal ulcer recurrence" because at least my review of the data -- that is why we end up with a difference at the end of 6 months. It is not that we are preventing the emergence of resistance that seems to occur in both groups. What we are doing is we are enhancing the eradication of the organism and thereby reducing the risk to subsequent occurrence. So, those would be my comments.

DR. FISHER: I am basically going to echo Dr. Craig's comments in that I think the wording needs to read, "in patients with active duodenal ulcer to reduce the risk of recurrence," again because I am still concerned about this one outlier study at 6 months, and 4 to 6 weeks is a short period of time. If we are looking for what we think Hp eradication really does with ulcer disease, I think it has to be over the longer term.

I also would just suggest that in any future studies they do -- one of the difficulties we had here this morning is the patients who did not heal at the end of therapy who were then not followed or looked at Hp status

and assessed, which I think, even though it is a small group, it is a group that needs to be looked at because it may be more common out there than not.

Dr. Butt?

DR. BUTT: I have kind of a question that might have to do with labeling or perhaps it is in the realm of practice. But since physicians are used to applying repeated courses of H2 blockers to patients who have duodenal ulcer disease, should there be some comment made about how many times this particular course of treatment should be given? Should it be given once or should it be given twice or three times? But perhaps that is projecting into the realm of practice and is inappropriate in a label.

DR. FISHER: We talked before. At the last meeting we said that it should be in proven ulcer disease with proven H. pylori infection. Should it be not just to say simply associated with H. pylori infection, but associated with proven H. pylori infection?

DR. BUTT: Yes, but if we have got proven H. pylori infection, many physicians are not going to have access to sensitivity data, and besides, we cannot agree on how to do the sensitivity data. And we may be dealing with resistant organisms. So, we will have a $700 course of therapy being given repeatedly to patients who in fact are

not benefitting from it except from the omeprazole component of the drug.

DR. FISHER: Dr. Judson?

DR. JUDSON: I think that is a very good point, and from everything we have seen with each successive treatment with clarithromycin, the likelihood that failures will increase and be owing to resistance will also increase.

So, I do not think we have any data to allow us to restrict that indication, but at some point that has got to be addressed. I would think it would be a very bad idea to continue to treat ulcer which we think is due to H. pylori with the same antimicrobial regimen that failed initially.

DR. FISHER: Dr. Comer and then Dr. Craig.

DR. COMER: I have two things.

One, on this issue perhaps we should see in the labeling patients who failed to respond to this therapy or who have a rapid recurrence, that this may represent emergence of microbial resistance and just leave it at that, and then the physician can at least think about it and choose an alternate regimen.

The other question I have is about this outlier study. I would like to know how many -- I call these

professional patients -- professional study patients. There are an awful lot of people running clinical trials that sort of re-enroll patients in multiple, multiple studies. I think that this is fraught with problems and may represent the reason why this study was different from the other three studies. I would be interested if the sponsor looked into that because I think that the patients who recur all the time and have been treated with multiple regimens and still get the Hp back or still get their ulcer back are not really representative of the usual patients that we encounter in practice.

DR. PERNET: I do not think we can get that information. Usually the trials by other sponsors are confidential and an investigator would not reveal what other study, what regimen a patient would be on. I do not think that is possible to obtain at this point.

DR. FISHER: Briefly.

DR. PIZZUTI: Just with respect to that question, though, the specific things we looked at in those patients that have bearing on your question, for instance, pretreatment size of ulcers, first episodes of duodenal ulcers, previous treatment with clarithromycin, and other GI diseases, and other GI and medication use, was all comparable among the treatment groups. There was not any

higher proportion in that group.

DR. FISHER: It is not among treatment groups. It is a question of one study versus the other study, that the outlier study had a different set of patients --

DR. PIZZUTI: It was still the same, relative amounts for those people in the other studies also.

DR. COMER: What was the percentage of professional patients?

DR. FISHER: Yes, I think I agree with the sponsor. You cannot get that data unless you just had a question, have you ever participated in a previous study about duodenal ulcer, period, without anything. And that does not break any confidentiality or anything, and it might be interesting in future studies to look at that.

Dr. Craig?

DR. CRAIG: In reference to the question about repeat courses of therapy, if you look at the data as presented by the company using the combination, resistance occurred in 84 percent of those that failed. If you look at the data that the FDA provided in which they looked at only those in which they had post studies, I think it was 25 out of 26, or 96 percent of them, that failed had resistant organisms. So, it would seem that one treatment would be what one would get with this combination.

DR. BUTT: Well, the problem is you end up with a patient with chronic active disease and the patient continues to be treated with, instead of omeprazole or cimetidine, this drug combination repeatedly, and doctors are very used to treating patients with ulcer disease, because we did not know about the relationship to H. pylori, chronically. I think that could be a major problem.

DR. FISHER: Dr. Judson, then Dr. Fanning, and then Dr. Megraud.

DR. JUDSON: I think we are back to that question, some wording. Because of the high likelihood of resistance and recurrent diseases, the same antimicrobial regimen should not be repeated. For clarithromycin in this case, treatment should not be repeated.

DR. FISHER: Dr. Fanning?

DR. FANNING: Yes. I wanted to respond to a couple of the things that were said. I think you have given us the kind of input we need and actually I have a draft statement that, after I make one other comment, maybe I could read as far as a potential indication and just have a show of hands. We certainly will deal with the labeling and package insert issues, but the discussion you are having is extremely helpful from that point of view.

As far as dealing with issues of repeated courses or resistance, those are things that we can incorporate into the label under cautions or things of that sort so that that information is available and is spelled out quite clearly.

DR. FISHER: Dr. Megraud?

DR. MEGRAUD: In case of treatment failure, you should indicate that it is necessary to culture the organism and to test the susceptibility to clarithromycin before repeating the treatment. I think it is important. Otherwise, you can go for 10 treatments.

DR. FISHER: I think that would be good to say, but as Dr. Butt says, to be realistic the people who are going to be seeing these people and treating them are the general practitioners out in the community and out in the hills and they are not going to get the Hp cultures. They may have no gastroenterologist for 300 miles around, and that may not be totally possible.

DR. MEGRAUD: It is maybe not possible in any case, but I am sure that in the United States it should be possible to get that in most of the cases.

(Laughter.)

DR. FISHER: Managed care may have a little to say about that.

While you are still drafting that, we have a second question here on this, which I think we need to go around the table.

DR. FANNING: Actually I am ready, if it is timely.

DR. FISHER: Absolutely fine. Go ahead.

DR. FANNING: This incorporates a couple of comments that people made, that the indication would read: "Treatment of patients with active duodenal ulcer to reduce the risk of duodenal ulcer recurrence associated with H. pylori infection." So, the change has been treatment of patients with active duodenal ulcer and then to reduce the risk of recurrence.

DR. LAINE: Are we going to accept that in all active duodenal ulcer patients who have H. pylori, the risk is high enough that we do not require any proof either serologically or endoscopically?

DR. FISHER: Well, the question is there, could you say associated with --

DR. LAINE: Could you say H. pylori infected patients, for instance?

DR. FISHER: Or reduce the risk of --

DR. LAINE: Treatment of H. pylori infected patients with.

DR. FISHER: -- infected patients with duodenal ulcer.

DR. FANNING: Okay.

DR. FISHER: So, it would be treatment of patients --

DR. FANNING: Of H. pylori infected patients.

DR. FISHER: -- with active duodenal ulcer associated with H. pylori infection to reduce the risk of ulcer recurrence. No?

DR. FANNING: No.

DR. LAINE: No. Treatment of H. pylori infected.

DR. FANNING: Treatment of H. pylori infected patients with active duodenal ulcer to reduce the risk of ulcer recurrence.

DR. FISHER: Sounds good to me.

Dr. Temple?

DR. TEMPLE: Well, we did not coordinate.

What would be the disadvantage of saying to eradicate H. pylori and then to add a sentence saying that elimination of H. pylori is associated with decreased recurrence rate? It seems a more direct statement of why you use an antibiotic. Just a thought.

DR. FANNING: Well, we are working on

redrafting that. That is an alternative and I would certainly like the committee's opinion on that.

DR. FISHER: Dr. Dunn?

DR. DUNN: We do not have the data to support that. We only have eradication in those patients who were healed.

DR. TEMPLE: You have said that a number of times, but other people have pointed out that you have healing in over 90 percent of the patients, so that even if you assume that the people who are not healed did not have eradication, you still have some knowledge of an eradication rate. You may not know precisely what it is, but it is not as though there is none there.

DR. DUNN: The one this afternoon is radically --

DR. TEMPLE: Just this one.

DR. DUNN: -- different, and part of what you are trying to do --

DR. TEMPLE: I understand.

DR. FISHER: Dr. Fanning or Dr. Temple, is that an alternative? Would you do it that way, or do you want a comment from the company on both? Because that is what it is really doing, is eradicating Hp. And that gets around the outlier study in a way too.

DR. COMER: Yes. I would be in favor of that.

DR. FANNING: Perhaps if we have the two statements, the one that Dr. Temple has suggested and the other, and just see a show of hands of which would be more appropriate from the committee's perspective.

DR. FISHER: Dr. Fredd?

DR. FREDD: Before voting on which one is better, as I heard it, it is the eradication endpoint that is convincing to the committee, not the endoscopic data. So, the indication for treatment of H. pylori positive patients with acute duodenal ulcer to eradicate H. pylori seems to me most direct in terms of the endpoint that was convincing, and the fact that eradication of the Hp reduces the risk of peptic ulcer recurrence falls back on the October meeting and the meta-analysis done and what we think that maneuver does.

I think this is terribly important for your consideration for endpoints in clinical trials in the future because if you do not have the Hp eradication statement as the link to benefit, then it may be we will rely more on -- it sounds like we might rely more on endoscopic data than eradication. So, personally from my point of view -- and it is strange coming from a non-ID person -- I prefer the Hp eradication within the

indication.

DR. COMER: Could we just do a show of hands, Rosemarie?

DR. FISHER: Yes, the first statement being the one that Dr. Fanning read initially which is a variation of the statement that is at the bottom of the page. Number two will be the revised statement as mentioned. Maybe we can just have an example of that then later written and circulated to the committee.

DR. FANNING: Sure, yes.

DR. FISHER: A show of hands on the voting members for number one.

(No response.)

DR. FISHER: A show of hands on voting members for number two.

(A show of hands.)

DR. FANNING: To eradicate H. pylori.

DR. FISHER: Forget the vote.

The first one would be in the treatment of patients of H. pylori infected patients with active duodenal ulcer disease to reduce the risk of duodenal ulcer recurrence.

The second one would be to eradicate -- the treatment of H. pylori infected patients with active

duodenal ulcer disease to eradicate H. pylori. H. pylori eradication is associated with the decreased risk of duodenal ulcer recurrence.

Number one, a show of hands.

(A show of hands.)

DR. FISHER: Dr. Dunn, and that is it.

Number two, a show of hands.

(A show of hands.)

DR. FISHER: Dr. Reller, I am sorry. Did I miss you before? It seems like Dr. Reller and Dr. Butt are abstaining.

DR. RELLER: I do not know what I am voting on. I think unless there are two or three statements that are clearly written out and put up on the board, we cannot vote on this.

DR. FISHER: All right. Let's do that then the first thing we come back after lunch, but I still want to do number two question here. So, if we can do that and put it on a transparency and just go around the table quickly. Thank you, Dr. Reller.

Question number two, should clarithromycin MIC breakpoints be established based on the bimodal distribution of broth dilution MICs from U.S. studies even though there are no approved testing methodologies for H.

pylori?

If yes, do you agree with the proposed breakpoints: susceptible, less than or equal to 0.064 micrograms per milliliter; intermediate, 0.12 to 2 micrograms per milliliter; and resistant, greater than or equal to 4 micrograms per milliliter?

Let's start with Dr. Elashoff.

DR. ELASHOFF: This is not an area that I know much about, but Dr. Reller's previous statement on this subject sounded very sensible to me.

DR. FISHER: All right. Dr. Banks-Bright.

DR. BANKS-BRIGHT: I agree with that. The last slides that were presented by the company went by too fast. There are too many permutations of this. I agree with Dr. Reller. I cannot vote on this. I would say no.

DR. FISHER: Dr. Rice?

DR. RICE: I am sorry. Since I have forgotten exactly what Dr. Reller said --

DR. FISHER: Dr. Reller, do you want to comment?

DR. RICE: I remember, but if he would clarify again, then I will state my concern.

DR. RELLER: I simply encouraged two things. One is that these be clearly delineated as tentative

breakpoints much like new data in NCCLS is put in bold. One of the difficulties, just for those who are not involved in this area regularly, is that once it gets into the package insert, as new data come along, it is very difficult to get it changed. Then one has NCCLS criteria and working world and then what is in the package insert.

So, as a preventive effort, I would urge whatever wording within the regulations, within the authority of the FDA to put in as tentative and, given that concept, that it be conservative, because of all the vagaries and the uncertainties of testing, to have what no one would argue with are on the outside as resistant and those that are incredibly susceptible and have broad intermediate range. And that is the sense, and what Dr. Utrup presented more closely matches that than anything else.

So, I would simply say that these make sense with the added proviso of putting in proposed tentative breakpoints -- the tentative concept.

DR. ELASHOFF: You also tied it to a specific methodology.

DR. RELLER: Exactly. They are tentative breakpoints with a broad intermediate for a specific methodology because of the impossibility of having multiple

methodologies using the same breakpoint that had never been verified as regards to the details of testing.

DR. FISHER: Dr. Rice?

DR. RICE: Thank you, Dr. Reller.

Having clarified your statement, I guess what I am voting is I agree with Dr. Reller. If I vote yes, then we assume that these are again temporary or tentative breakpoints until there is agreement per NCCLS and inter-laboratory reproducibility standards, that these are to be the -- I should not say permanent -- the agreed upon breakpoints.

Again, I would still urge the sponsor to consider looking more closely at the question of resistance relative to these breakpoints.

DR. FISHER: Dr. Utrup?

DR. UTRUP: I would be happy to put in the words "tentative breakpoint" in the label.

DR. FISHER: Dr. Judson?

DR. JUDSON: Yes, I agree with the proposed tentative breakpoints.

DR. FISHER: Dr. Butt.

DR. BUTT: I agree with Dr. Reller.

DR. FISHER: Dr. Dunn.

DR. DUNN: I agree with Dr. Reller.

DR. FISHER: Dr. Comer.

DR. COMER: I basically agree that we should say that there are no approved testing methodologies and then highlight Dr. Graham's method with the tentative breakpoints.

DR. FISHER: Dr. Craig?

DR. CRAIG: I think it is especially important, if we are going to put some cautionary words about retreatment and especially if we are going to try to encourage them to test the organism, that we have some tentative breakpoints. I would agree with these especially if you are going to give a specific method. If you were not going to give a specific method, I might increase it up to .25 since it looks like Mueller-Hinton, which is a more common tested media, is shifted about twofold over, so that then you would, at least for those people using that type of methodology, still call susceptible organisms susceptible.

DR. FISHER: I am going to agree with Dr. Craig's modification of Dr. Reller's comments.

DR. KIRSCHNER: I am going to agree with the word "tentative," but I just think maybe some statement about the lack of any clear method would be useful to people who are not in this meeting and not hearing this

whole discussion.

DR. NORDEN: I never thought I would be more conservative than Barth, but I am very concerned. I would vote no. I really do not think we have guidelines yet to establish breakpoints. However, I am also am moved by the fact that if people are going to do testing, that they need something and I would go along with the tentative. But to answer the first question, I think the answer is no.

DR. FISHER: Dr. Bertino?

DR. BERTINO: I would vote no also because I think there are too many unanswered questions about susceptibility and resistance and response and also the dynamics of these agents.

DR. FISHER: Dr. Reller, any additional comments?

DR. RELLER: We skipped over 1B earlier and I think at some point it is very important to come back to. Given the uncertainties and what I have already said about these and the tentative emphasis, the reason that I feel we ought to have something is the incredible association of recurrence and persistence with organisms in the bimodal distribution that are different, not only different, but they are different from what one started with. There are very few instances where one can so clearly associate

clinical failures with resistance that comes about after initiation of therapy.

It has been pointed out earlier in practical terms, this or any other regimen is most often, outside of the study setting, going to be initiated based on clinical symptoms, endoscopy, but it is not going to be based on isolation of the organism and pre-therapy susceptibility testing.

Given that reality, I think we need to get into this indication, et cetera, and caveats that if a patient fails, if they are in the 40 or 50 percent of patients at 6 months who have failed, that just doing the same thing again is not going to be good enough and that those patients, wherever possible, should have this organism because it is very likely, if it is present, it is going to be resistant and something else is going to have to be done.

By having the concept that resistance develops and there needs to be some -- and this is a first pass -- I think it just puts the emphasis where it belongs, that failures are owing to resistance and you cannot talk about resistance unless you have at least some method that may reasonably accurately for a first pass categorize them into these two diverse populations.

That is why I vote on the broad intermediate, the tentative, but something so that we can come back to 1B and say if you fail, it is probably owing to a resistant organism.

DR. FISHER: Dr. Megraud?

DR. MEGRAUD: I fully agree with the breakpoints proposed by Dr. Utrup. This corresponds to our experience in France. I think that a broad intermediate zone is important to get up to now, but also I agree with Dr. Reller that this must be noted as tentative breakpoints because the NCCLS or other organizations may have to come back on that in the future.

But I have one question for you. Why do you want to have breakpoints if you expect that nobody will use it?

DR. FISHER: That is a very good question.

Can I just ask Dr. Reller a question? We skipped 1B because we all sort of went to a yes of things, but I would just like to ask, we have all been hinting at little things around the table. What sort of additional studies -- and I do not want to get into a long thing. I want people to be very brief if they have any, very directed. We have heard some already. They are in the minutes and in the transcription. I would ask you not to

repeat any additional studies that you have already mentioned that you would like to be done, but I will just go around the room real quickly and ask are there any additional studies or data that are needed from what people have already mentioned. Dr. Elashoff, Dr. Banks-Bright, Dr. Rice, Dr. Judson? Dr. Rice. I am sorry.

DR. RICE: I am sorry to belabor the point. It is not an additional study per se. I just wanted to make the point following up to the question that our French colleague had.

I think the whole point gets back to the practical application, whatever comes out of this advisement, is that the majority of general practitioners and physicians will probably not be doing cultures. So, it gets back to the onus is on the sponsor I think to strengthen the package insert question around the repeated utilization of this regimen if approved for the indications we have discussed, that physicians or providers be continuously educated that they cannot continue to treat and retreat using the same regimens. That is my comment.

DR. JUDSON: One of the issues that we brought up in the October meeting is our, I think, appropriate concern of ever being able to use monotherapy for an infection that has a huge bacillary load. It is a little

bit potentially equivalent to treating well-established TB with a single drug. I think what we are seeing already in terms of failures and the association with resistance is just confirming that. So, in terms of future research, other synergistic probably combinations of antibiotics may really be required to go beyond the cure rates that we have experienced so far.

DR. FISHER: Dr. Butt, Dr. Dunn, Dr. Comer?

DR. COMER: I was told by Dr. Fredd that I could not recommend a study that looked at Hp eradication using a breath test because the breath test is not yet approved, but the principle remains that the patients who are unhealed in these studies we would like to see what the eradication status is of those patients.

DR. FISHER: Dr. Craig?

DR. CRAIG: Yes, the same thing. I would want to see eradication rates in those that do not have active ulcers.

DR. FISHER: That is almost a different question I think. What Gail is asking for is eradication in patients who do not heal as opposed to people who do not have active ulcers and eradication rates. I agree with both of those comments.

Dr. Kirschner?

DR. KIRSCHNER: Well, the studies I would like to see obviously are not done in this forum and that is comparative studies of several regimens simultaneously so that we really have an idea about which regimens are best.

DR. NORDEN: I would like to see the follow-up of some of the patients with resistant organisms to see, one, if resistance persists and, two, whether there are any who revert and what happens to them in terms of ulcers.

DR. FISHER: Dr. Bertino, Dr. Reller?

DR. RELLER: I am concerned over time that what is a regimen for initial treatment may be in the order of 50-60 percent effective given that most patients will not have the organism isolated initially may dwindle to 40 percent, 30 percent, 20 percent, 10 percent, as the proportion of resistant organisms in the population may for whatever reason -- use of erythromycin, clarithromycin for other purposes -- go up, so that some way to assess whether the efficacy remains in the range expected, it seems to me, would be very important. And this would apply to other potentially approved regimens because it may come about in fact that before initiation of any regimen, one would need to isolate the organism and do susceptibility testing, much as we do with other infections.

The only reason practically we probably will

not be doing that now is patients do not present -- they present because they have pain and because they have an ulcer, not because they have a diagnosis of H. pylori infection. That is an assumption and a reasonable one. But when we have 98 percent or so susceptible, we do not need to do it except for the failures. But I am worried that maybe that would change in the future.

So, I think post-marketing to assess whether the general overall success rates for initial use of this or any other regimen are maintained in the area that you would expect and then to look intensively at the failures with alternative regimens and to get susceptibility testing as has been mentioned before.

DR. FISHER: Dr. Megraud and then Dr. Botstein?

DR. MEGRAUD: I do not think that the use of macrolides in general, in clarithromycin especially, for respiratory track infection, for example, will have a big impact on the resistance to H. pylori. In our country in France, this last 10 years there was wide use of these drugs, macrolides, and the resistance of H. pylori remains around 10 percent in spite of that. I am not sure it would be the same if we focused the treatment on H. pylori as it is proposed today with this regimen.

The study I would like to see do exist include

another antibiotic in association with clarithromycin and allows to eradicate in about 90 percent of cases.

DR. FISHER: Dr. Botstein?

DR. BOTSTEIN: Right now when a patient walks in the door to be treated for an ulcer, most such patients will have an organism that is susceptible to clarithromycin. That may well change in 5 years, in 10 years. Would the committee think it reasonable to ask the sponsor to do some kind of sampling in the community of rates of resistant organisms and put it in the labeling now versus 5 years, 10 years, whatever time period seems reasonable so that the practitioner could get at least a rough idea of rates of resistant organisms that might be expected in a new patient?

DR. FISHER: We have passed around to the committee the two statements. I have been asked to summarize what the vote has been on the comments.

Basically at first, yes, the combination therapy has been approved for the indication that we will vote on now. People have it in front of them. There is one statement that is missing in front each of these which is that "the combination therapy of omeprazole and clarithromycin is indicated for the."

Then, one, treatment of H. pylori infected

patients with active duodenal ulcer to reduce the risk of duodenal ulcer recurrence, or two, that the combination is indicated for the treatment of H. pylori infected patients with active duodenal ulcer to eradicate H. pylori. H. pylori eradication is associated with the decreased risk of duodenal ulcer recurrence.

Can I have a show of hands for number one? Dr. Reller?

DR. RELLER: Excuse me. I should like to request that you put a third statement on which is simply the statement as written. The reason for that is that patients present and physicians initiate treatment in the current environment, or would probably in the current environment, based on pain and an ulcer and they do not know whether they have H. pylori or not at that point. We know the pathophysiology. We know the reality.

DR. FISHER: I agree with you. The question is would it be more acceptable to say treatment of patients with active duodenal ulcers infected with H. pylori?

DR. BOTSTEIN: Or do you want presumably Hp infected?

DR. FISHER: I do not want presumably Hp infected because that opens up the whole NSAID associated ulcer group to be treated with this combination without

being tested. Personally I would not be in favor of that.

Dr. Judson?

DR. JUDSON: One and two are really identical except that two presumes that the reader does not know that recurrences are associated with H. pylori, and the question is how far we want to go in attempting to educate with the indication.

DR. FISHER: Do we want to try --

DR. COMER: Can we vote please?

DR. FISHER: Okay. The third statement being just as it is printed there or as I amended it in the last --

DR. RELLER: I would recommend just as it is printed because quite honestly, I think that it is very difficult, if not impossible, in a committee this size or group to get down every last word, and moreover, that is the prerogative of the agency.

DR. FISHER: Okay.

DR. RELLER: I think it is the sense. It is because of the sense of the issue and the way physicians treat patients that I had encouraged you to consider the third statement as it is and leave the details to the agency.

DR. FISHER: Dr. Fredd, a quick point?

DR. FREDD: And the sense of the difference to me is not whether there is an association between H. pylori and ulcers, but whether the maneuver is to eradicate H. pylori and from that follows something else. I am somewhat concerned if we do not agree, as you did in October, that eradication is the endpoint which, if it shows effectiveness, is presumed to show less ulcer recurrence. If we do not focus on that as the endpoint of this and future such trials, we may go back to endoscopic considerations.

In the first indication, if you do not have that in there, could we as an agency go back and say, well, the endoscopy did not work out in the second U.S. study, so therefore we do not have two studies? I am a little bit concerned about making sure that the committee and the agency agree that eradication is the endpoint, and that is emphasized in the second --

DR. FISHER: Okay.

Let's go for a vote for number one.

(No response.)

DR. FISHER: No one.

Vote for number two?

(A show of hands.)

DR. ELASHOFF: Are we voting on three?

DR. FISHER: We are voting on three. This is number two.

DR. ELASHOFF: Right, but we are voting on three questions.

DR. FISHER: We are voting on three statements.

Number two. This is Dr. Elashoff, Dr. Banks-Bright, Dr. Rice, Dr. Judson, Dr. Butt, Dr. Comer, Dr. Craig, myself, Dr. Kirschner, Dr. Norden, Dr. Bertino. Okay.

Statement number three as stated initially.

(A show of hands.)

DR. FISHER: Dr. Dunn and Dr. Reller. Two.

So, the vote was for approval with 11 for number two and 2 for number three.

The other comment that was asked to clarify on susceptibility testing is that there was 11 for Dr. Reller's suggestion of setting breakpoints but with a broad intermediate range with "tentative" being put in the guidelines, and 2 were against setting that point as we stand.

At that, we are going to call this session to an end. I would like people to be back here at 1:20 to start and we will go from there. Thank you very much.

(Whereupon, at 12:20 p.m., the committee was

recessed, to reconvene at 1:20 p.m., this same day.)

AFTERNOON SESSION

(1:24 p.m.)

DR. CRAIG: We are starting approximately -- it looks like we have lost about 2 hours from our original schedule. Everybody for the Glaxo Wellcome presentation are trying to make theirs as concise as possible, and to also sort of speed up the process, we will not entertain any questions until all of the speakers for the Glaxo Wellcome presentation have given their presentation.

So, start it off with Andrew Gustafson.

DR. GUSTAFSON: Yes. Thank you, Dr. Craig.

Dr. Fisher, Dr. Craig, members of the Anti-infective and Gastrointestinal Drugs Advisory Committees, good afternoon. I am Andy Gustafson, Director of Regulatory Affairs for Glaxo Wellcome. We are very pleased to be back once again before this joint advisory committee.

Today we are here to review data from our new drug applications for ranitidine bismuth citrate and its safe and effective use with the antibiotics clarithromycin and amoxicillin. These regimens are proposed for the treatment of duodenal ulcers in patients infected with H. pylori.

Before I go too much further, I just want to

point out that I will be using the acronym RBC when referring to the chemical entity ranitidine bismuth citrate.

First I would like to review the agenda for our presentation. I will begin with an introduction. Then Dr. Russell Williamson of Glaxo Wellcome R&D will present the microbiology of RBC alone and in combination with antibiotics. Next Dr. Art Ciociola, Director of Gastroenterology, will review our clinical research program and summarize the efficacy data. This will be followed by a presentation of the worldwide safety database by Dr. Duane Webb, our International Director of Gastroenterology Clinical Research. Dr. Pete Peterson, Professor of Medicine at the University of Texas Southwestern Medical Center, will then follow with a discussion of the risks and benefits of RBC and Dr. Webb will then return to the podium for a brief conclusion.

Now, on December 29, 1994, Glaxo Wellcome submitted three applications to the FDA for RBC. NDA 20-558 for RBC and amoxicillin and NDA 20-559 for RBC and clarithromycin were submitted for the treatment of duodenal ulcers in patients infected with H. pylori. These two co-prescription NDAs are the subject of today's meeting and are currently under review within the FDA Division of Anti-

infective Drug Products.

NDA 20-557 was submitted for RBC alone in the treatment of active duodenal ulcers and is currently under review within the FDA Division of Gastrointestinal and Coagulation Drug Products. Although this last application is not the subject of today's meeting, we do plan to present the safety data from this application as it is relevant to our discussion of the co-prescription NDAs.

Chemically RBC is ranitidine bismuth citrate, a novel salt of ranitidine complexed with bismuth and citric acid. Each 400 milligram tablet of RBC contains the equivalent of 150 milligrams of ranitidine, the approved dose of Zantac for the treatment of active duodenal ulcers, and the equivalent of 128 milligrams of elemental bismuth.

As I have already mentioned, I will be using the acronym RBC and our speakers may also use the trade name Tritec when referring to the compound.

With regard to its mechanism of action, RBC is a unique agent that possesses the acid suppression properties of an H2 receptor antagonist, together with the cytoprotective and anti-H. pylori activities of bismuth. When used with clarithromycin or amoxicillin, RBC eradicates H. pylori infection.

Now I would like to review the proposed

labeling for RBC. As you will hear from our speakers today, we submit that RBC is both safe and effective for the following indication and usage claim. Here again I will use the trade name Tritec.

"Tritec, when used in conjunction with clarithromycin or amoxicillin, is indicated for the treatment of H. pylori associated duodenal ulcers. This therapy has been shown to increase the overall success of treating duodenal ulcers, as defined by ulcer healing and eradication of H. pylori with no ulcer recurrence."

With regard to our dosage and administration claim, we propose the following. "Patients should be treated with Tritec 400 milligrams b.i.d. for 4 weeks and clarithromycin 500 milligrams t.i.d. for the first 2 weeks. An alternative regimen is Tritec 400 milligrams b.i.d. for 4 weeks again, and amoxicillin 500 milligrams q.i.d. for the first 2 weeks. This alternative regimen may be used for patients who are allergic to or unable to tolerate macrolides and for patients whose H. pylori infection is resistant to macrolide therapy."

I would like to conclude by acknowledging that there is an enormous amount of data contained in our applications for RBC. Our presentation today is designed to provide you with the most important data from these

applications.

We are also prepared to address any questions that this advisory committee might have with regard to the data. We believe that this will give you the information that you need to address the questions that FDA has posed and also enable you to reach the conclusion that these RBC regimens are indeed safe and effective for the treatment of duodenal ulcers in patients infected with H. pylori.

I just want to mention, before closing finally, that in order to facilitate the Q&A discussion at the end, our speakers have included a number on their slides which appears in the upper right-hand corner. So, as we go through this, you may want to write that number down and refer back to it.

Ladies and gentlemen, thank you for your attention. I would now like to turn the podium over to Dr. Russell Williamson.

DR. WILLIAMSON: Ladies and gentlemen, monsieur, the eradication of H. pylori requires a therapy that not only inhibits the growth of the organism, but actually kills it. In addition, the therapy should overcome the increasing problem of resistance to some currently available antibiotics.

RBC was synthesized in May of 1988 as a novel

salt with combined anti-ulcer and anti-H. pylori activity, and this afternoon I will present the key microbiological findings relevant to the eradication of Helicobacter pylori with RBC, in particular, that RBC kills H. pylori, that RBC plus a single antibiotic, dual therapy, is even more effective at killing H. pylori, that the synergistic increase in killing occurs even in strains apparently resistant to the antibiotic, and that finally, RBC may actually diminish the emergence of resistant strains.

To demonstrate the anti-Helicobacter activity of RBC, we did a series of agar dilution experiments, and this particular slide shows the control where we have 20 different clinical isolates of Helicobacter pylori actively growing on an agar plate which does not contain any antibiotic. We have a Staph. aureus up here and we have four isolates of E. coli. To achieve that amount of growth, we need to incubate those plates for 3 days.

On this slide I demonstrate what happens to Helicobacter pylori when incubated with RBC at a concentration of 16 micrograms per ml, and in contrast to the previous slide, we actually only have one or perhaps two active growth of H. pylori. This is just an imprint of the inoculator. You will be aware that the Staph. aureus and the E. coli are actually unaffected by this

concentration of RBC.

Again in contrast, this is a plate that contains bismuth citrate at the same molar concentration of bismuth, 16 micrograms per ml. What we see here, again the control organisms up here are actively growing, but we see here at least 5 or 6 of these 20 organisms and -- sorry -- 5 or 6 actively growing and 4 or 5 staggering a little bit. So, when we compare RBC with bismuth citrate on its own, quite clearly RBC has an increased activity against H. pylori.

Now, of course, growth inhibition does not tell you anything about the cidal activity of the agent. Now, we have established the RBC is active and indeed 16 micrograms per ml inhibit over 95 percent of the strains. We have never observed resistance to bismuth. Indeed, other individuals have not either. These concentrations of bismuth are achievable at the site of colonization or infection within the stomach because of the inherent solubility properties of RBC. As I say, the eradication of H. pylori requires agents that are cidal because we want to eradicate and not to suppress H. pylori.

A demonstration of the killing effect of antimicrobial agents is always shown by a killing curve. We start off with a large number of bacteria per

milliliter. Here we have got approximately 10 million viable bacteria, 10 to the 7th. Under control conditions with no agent, they actively grow over the period of experiment, up to 30 hours here, and we see that ranitidine, which was commented on earlier this morning, has no anti-H. pylori activity that is significant, MICs well above 500 micrograms per ml, no growth inhibition.

In contrast, bismuth citrate may have a slight suppressive activity, but the admixture of ranitidine plus bismuth citrate is no more effective than either of these agents. In complete contrast, the same molar concentration of ranitidine bismuth citrate has a clear and significant decrease in the viability of this organism. This we believe is due to the solubility characteristics of RBC which are very different from bismuth citrate.

Now, you will observe that although the vast majority of H. pylori are killed, not all organisms are killed. Therefore, we looked at the effect of combining RBC with a single antibiotic, and we used a range of antibiotics that are in clinical use for the eradication of H. pylori.

Now, in contrast to many standard microbiological techniques, we did not look for synergy or additive effects by merely looking for growth inhibition

because we are interested in killing and wiping out the organism. So, we looked at the quite complicated but necessary total kill of H. pylori by the combinations. Out of all the studies that we did, we found that there was an extreme synergistic activity with several agents, of which clarithromycin was the best.

I demonstrate this in the next slide in which we chose a deliberately low concentration of RBC. This is a quarter of the MIC for this particular organism. When we added the MIC concentration of clarithromycin, we begin to see a cidal activity, but it is when we combine both agents at these concentrations 2 and 0.06 per ml that somewhere between 6 hours and 24 hours exposure we see the complete and total killing of H. pylori, an example of synergy between these two agents.

Now, of course, this is a plot. It measures the amount of interaction throughout time using a fixed combination of agents. Now, one of the most powerful techniques available to microbiologists is that of the two-dimensional checkerboard technique, and just to run through this type of technology for those of you who are not familiar with it, what we are using is a microtiter based system in which in one dimension -- let's say from this end here going up to the top right -- we are decreasing in

twofold steps the concentration of one agent. Here we have decreasing concentrations of clarithromycin.

Again, starting in this set of rows going in this dimension now, we are diluting out the concentration of RBC such that the well in this corner has the highest concentration of both agents. The wells in these extremities have the highest concentration of each agent on its own, and in the opposite corner over here, we have a well with no antimicrobial agents whatsoever.

Helicobacter pylori was inoculated into these wells and we took out samples after 24 hours exposure and then plated those onto agar plates that did not contain any antibiotic because we were not interested in merely looking at the inhibition of growth but the killing of H. pylori by these combinations.

Now, where we see the very high columns up here, there was no killing, no growth inhibition whatsoever. In contrast, where we have a square shown on these plates here, there was total and complete killing of H. pylori in that particular combination.

Now, as I showed you in the previous slide, 2 micrograms of RBC and 16 nanograms gives us complete kill. But you see here there are 19 different combinations of RBC and clarithromycin that give the complete kill of H.

pylori, and you will note that neither RBC on its own or clarithromycin on its own is able to kill H. pylori, an example of synergy.

Now, we were hearing this morning about the amount of clarithromycin available to kill H. pylori at the site of infection. The data suggested up to 4 micrograms per ml in non-acid suppressed individuals. I would like to point out that we observed synergy down to 1 nanogram per ml of clarithromycin in the presence of RBC. This is 4,000-fold less than the concentration achievable at the site of infection.

Now, the question of resistance to antibiotics is very pertinent to eradication of H. pylori. There is increasing data in the literature that if you have a resistant organism, it is very difficult to get rid of it. Now, the resistance can be acquired either before therapy, and there is increasing evidence, as we heard today, of eradication therapy in the failures actually leading to resistance acquisition.

From our own studies and from the literature, there has never been resistance reported to either bismuth or amoxicillin. Indeed, there is no beta-lactamase activity in H. pylori. However, resistance to the nitroimidazoles or the macrolides is present in individuals

either going into therapy or has been selected out during therapy.

Now, we have in vitro laboratory data that clearly shows that RBC has synergistic activity against organisms that are resistant to an antibiotic before therapy were to begin. In addition, we have again generated data in the laboratory that RBC actually diminishes the emergence of resistant organisms in vitro. So, this would suggest that we could treat patients who have organisms already resistant as well as prevent resistance during therapy.

As I have shown in this slide here, this is an organism of Helicobacter pylori from an individual who had an ulcer, and this organism is 500-fold less susceptible to clarithromycin than most populations of Helicobacter pylori. When we add the MIC concentration, we see a small decrease in the viability of the organism. But again, in complete duplication of the result with the susceptible strain, when we add clarithromycin and RBC, again at some point between 8 hours and 24 hours, we find complete and total killing of this "resistant" organism.

To demonstrate that RBC could actually affect the spontaneous acquisition of resistance, we took two clinical isolates from individuals with duodenal ulcer

disease from the U.K. and repeatedly subcultured them both with and without RBC at half its MIC concentration for up to 22 subcultures, and this clearly took a period of 2, 3, or 4 weeks.

At five or six occasions during that subculture, we determined the spontaneous resistance rates within those populations of bacteria. This was done by selecting out the mutants that were resistant on agar containing antibiotics, so we were able to numerate the total number of resistant organisms that were being selected out, compared with the total viable count within the population of H. pylori.

And as clearly demonstrated on this slide, pre-growth of these two organisms with RBC diminished in three out of the four cases the ease of acquisition of resistance. So, pre-growth of these organisms with RBC statistically reduced the emergence of resistance in those populations of bacteria.

Thus, in summary, RBC is indeed not only able to inhibit the growth of H. pylori, but indeed kills it. It is bactericidal. This killing activity is indeed increased, is potentiated in the presence of clarithromycin against strains that one would consider susceptible to clarithromycin, but more importantly against organisms that

would appear to be resistant to clarithromycin. Finally, RBC may actually diminish the resistance acquisition during therapy which could therefore positively affect the environmental impact of eradication therapy.

Thank you for your attention. I would now like to pass it over to Dr. Art Ciociola who will present the efficacy results with RBC.

DR. CIOCIOLA: Thank you, Dr. Williamson. When I put this talk together, they told me that I had to stick with the script, and my script says "good morning," so I need to wish you all good morning.

(Laughter.)

DR. CIOCIOLA: Before I begin my comments and my presentation, I just want to share with you some thoughts. I have been listening very intently this morning to your comments, your questions about these type of data. I have been struggling with these data for the past two years. It is a very difficult concept to grasp in this time period, but what I want to do, I hope, is to address some of your comments and concerns that you raised this morning in my presentation. If I have not done that, I will certainly answer your questions later.

My overall objective for this presentation is to prove that RBC in combination with clarithromycin and in

combination with amoxicillin is effective in the treatment of patients with H. pylori associated duodenal ulcer disease.

Now, since I feel this meeting is really a continuation of the meeting we just had two months ago, I just wanted to briefly summarize for you the major points from that meeting. I will then give an overview of our clinical investigations and the efficacy of the data we have generated in the conduct of these studies.

Now, I think as we all remember, the three major points we agreed on was that H. pylori eradication is the primary endpoint in assessing the reduction in ulcer recurrence. We agreed there was no minimal level of treatment efficacy that could be established at this point in time, and that drugs can only be approved for use in patients who have been studied.

Now, building on these agreements, I would like to discuss the efficacy of RBC plus antibiotics. I have structured my presentation to be able to address the questions that have been posed to you by the FDA, particularly about the efficacy of RBC when used in conjunction with clarithromycin and amoxicillin.

The first question. Do these clinical trials demonstrate the effectiveness of the combined regimen of

RBC plus clarithromycin or amoxicillin in patients with active duodenal ulcer? Today I will show you data that will allow you to conclude that we have, indeed, proven the efficacy of these two treatment regimens.

Now, if the first answer to that question is yes, on which endpoint should the indication for the product be based? We will show you data that RBC plus clarithromycin eradicates H. pylori infection in up to 94 percent of patients.

Now, for the overall success endpoint, we will show you data that RBC plus clarithromycin or amoxicillin significantly improves overall success rates.

Finally, do the clinical studies or other supporting data demonstrate that each component of the regimen contributes to the claimed efficacy? We will show you data from our studies and the literature that demonstrate the relative contribution of each of the components to the claimed effects.

Now, let's begin to answer these important questions.

In 1988 we set out to develop a treatment for duodenal ulcer patients that would heal ulcers and prevent ulcers from recurring through the eradication of H. pylori. We developed RBC because the ranitidine component possesses

these well-known pharmacologic properties that include active acid suppression, symptom relief, and ulcer healing. Now, the bismuth component of RBC also provides ulcer healing possibly through cytoprotective mechanisms, but more importantly, bismuth has been shown to have anti-H. pylori activity.

Now, what is the rationale for combining RBC with an antibiotic? It is well know that antibiotics are bactericidal against H. pylori both in vitro and in vivo, and we were interested in clarithromycin because it is the most effective single agent against H. pylori studied to date. We are interested in amoxicillin as an alternative regimen because it is effective but does not induce resistant organisms.

Now, when we combine RBC with an antibiotic, we have observed these combinations to show synergistic activity against H. pylori. In addition, we have reported in vitro data suggesting that this combination may be effective against resistant strains and may prevent the emergence of resistant strains of H. pylori.

Finally and most importantly, this combination provides the patient with a very simple, convenient dose regimen that will effectively heal ulcers, eradicate H. pylori, and reduce the rate of ulcer recurrence. These

regimens only have 5 to 6 tablets per day as compared to other treatment regimens that may require up to 16 tablets per day.

Now, this leads us to our program objective. The objective of this clinical program was to demonstrate that RBC plus an antibiotic is safe and more effective than RBC alone, the antibiotic alone, and placebo in the healing of duodenal ulcers and preventing the ulcers' recurrence through the eradication of H. pylori.

Now, to accomplish this objective, we only enrolled patients with active duodenal ulcer disease, and we assessed those patients for ulcer healing 4 weeks after treatment. We then followed those healed patients for 6 months to assess for their continued ulcer healing or maintenance of ulcer remission. This we defined as our clinical cure.

In addition, we followed healed patients to establish eradication of the infection. This was defined as our microbiological cure. Therefore, the primary criteria to establish the efficacy of the treatment is complete overall success, and we have defined that as ulcer healing, eradication of H. pylori with no ulcer recurrence.

This next slide is a schematic diagram of our basic study design. We chose this design because it

enabled us to measure ulcer healing and ulcer relapse rates in the entire randomized patient population. Now, we presented this design to the Gastrointestinal Drug Products Division in 1991 for their review.

Now, let me review briefly some of the major elements of this design. During the screening phase, patients with suspected duodenal ulcers are endoscoped to confirm the lesion. Those patients with a confirmed lesion were assessed for H. pylori infection. They were then randomized to study treatment for 4 weeks, and they received the antibiotic during the first 2 weeks of that 4-week period. Patients were endoscoped at the end of treatment to confirm ulcer healing and again assessed for H. pylori status.

Healed patients were then followed for up to 6 months while receiving no further medical treatment. Endoscopies were performed at 1, 3, and 6 months to again assess for ulcer relapse and H. pylori. Unhealed patients at the end of the treatment period were considered a treatment failure and were no longer followed. Patients with an ulcer relapse during the follow-up period were also considered treatment failures and no longer followed.

Let's talk about the patient population. The patient population in our studies were patients with an

endoscopically diagnosed active duodenal ulcer. This decision was based on numerous studies that have been conducted over the past decade that have suggested a strong causal relationship between H. pylori and duodenal ulcers.

The ulcer was defined as a break in the mucosa with perceptible depth that ranged in size from .5 to 2 centimeters at the longest diameter. The lesion must be located in the duodenum, duodenal bulb, or the immediate post-bulbar duodenum.

Now, at the time we designed these studies, the relationship between H. pylori and peptic acid disease was being actively debated, so we enrolled all non-NSAID duodenal ulcer patients to be able to assess for other factors that may have been involved in ulcer healing and ulcer relapse. Therefore, we designed our study so that central laboratory personnel could perform all H. pylori assessments blinded to study treatment and the study visit. This resulted in the patients' pre-study H. pylori status being blinded until study completion.

Now, in an effort to ensure a homogeneous patient population, we only enrolled patients who had denied recent NSAID or corticosteroid use. We attempted to exclude these patients whose ulcer disease may have been caused by these particular drugs. In addition, as shown on

the slide, the use of compounds known to heal ulcers or affect H. pylori were also limited in the 30 days prior to study enrollment.

Now, the U.S. program consisted of two factorially designed studies with each antibiotic. The first two studies assessed the efficacy of RBC plus clarithromycin and are number H2B-305 and 306. The second set of studies assessed the efficacy of RBC plus amoxicillin and are numbered 303 and 304. In each of those studies, between 172 and 204 active duodenal ulcer patients who were either Hp positive or Hp negative at pre-study were enrolled in each of these studies.

This slide shows the four treatment arms for the four U.S. studies. As I indicated earlier, they were fully double-blind factorial designed studies. These studies were designed to compare the combination treatment regimen -- that is, RBC plus the antibiotic -- to the components of that combination -- that is, RBC alone and the antibiotic alone.

Now, the four treatment groups for 303 and 304 consisted of RBC 400 milligrams twice a day plus amoxicillin 500 milligrams four times per day compared with RBC alone, amoxicillin alone, and placebo. Similar treatment groups were used for the 305 and 306 studies.

Treatment arms were RBC 400 milligrams twice a day plus clarithromycin 500 milligrams three times per day, and these were compared to RBC alone, clarithromycin alone, and placebo.

Now, there were four similarly designed non-U.S. studies which are numbered T08 through T11 respectively. Studies T08 and T10 used three treatment arms, RBC 400 milligrams twice a day compared with RBC 400 milligrams plus amoxicillin or RBC 800 milligrams twice a day plus amoxicillin. Now, studies T09 and T11 substituted clarithromycin 250 milligrams four times per day in place of amoxicillin.

This next slide shows the assessments for H. pylori to diagnose the infection and document eradication. They were based on the March 1995 draft Points to Consider document prepared by the FDA Division of Anti-infective Drug Products. Diagnostic tests performed in our studies included the CLO test, culture, and histology. In two of the four non-U.S. studies, T08 and T09, the urea breath test and CLO test were performed.

Now, to be considered infected with H. pylori, all patients must have had either a positive culture growth or a positive CLO test and histology. In the two non-U.S. studies where the urea breath test was done, those patients

had to have a positive CLO test and a positive urea breath test.

Now, eradication was defined as having at least two of these tests performed at least 28 days post-treatment with all tests being negative. No test could be positive.

Now, in regard to sample size of these studies, these studies had adequate sample size to detect the primary treatment comparison differences.

Let's move on to the statistical aspects. H. pylori eradication was assessed in patients who were confirmed H. pylori positive at pre-study. This parameter was defined as the proportion of patients who were H. pylori negative by the combined H. pylori assessments at least 28 days post-treatment. All treatment comparisons were made by Fisher's Exact Test.

However, more importantly is our primary efficacy parameter of complete overall success. This parameter analyzed confirmed H. pylori positive patients at pre-study. It was defined as the proportion of patients whose ulcers healed and were eradicated of H. pylori infection with no ulcer relapse. Treatment comparisons were primarily made by the life table extension or the Mantel-Haenszel test. Treatment comparisons were further

supported by the Mantel-Haenszel test for crude and modified-crude rates.

Now, the criteria for effectiveness for these studies was to demonstrate that RBC plus clarithromycin or amoxicillin have significantly higher H. pylori eradication and complete overall success rates as compared to RBC alone, the antibiotic alone, and placebo. In addition, we sought to demonstrate the contributions of each of these components of the therapy as in RBC alone, clarithromycin alone, or placebo, particularly to the claimed effects of eradication and complete overall success.

Now, to support the first question that has been posed to you by the FDA regarding the efficacy of RBC plus clarithromycin, the supporting data are shown in this next series of slides.

This slide shows the patient disposition in each of the four studies. The first line shows the number of patients enrolled in each study with an active duodenal ulcer. The second line identifies the number of patients who had valid H. pylori tests performed and who were confirmed H. pylori infected at pre-study. For example, the first study, 305, on the left, 136 of the 185 patients tested were H. pylori positive at pre-study. 84 of those 136 patients healed after 4 weeks. 76 entered the follow-

up period, and 68 completed that follow-up phase.

Now, this next slide is a summary of the patient demographics for the two U.S studies. We did not observe any significant differences between treatments with regard to gender, age, race, tobacco use, or ulcer history.

Now, one concern with treatment regimens for H. pylori is patient compliance, particularly with some of these difficult regimens. However, with the RBC plus clarithromycin regimen, only 5 tablets per day are required, and the patient compliance data is shown on this slide. We observed the patient with this regimen was very good. Over 85 percent of the patients were 80 percent compliant for both RBC and clarithromycin.

Now I would like to show you the efficacy data in the order in which the data are generated in the clinical study. First I will show you the rates of ulcer healing; second, rates of eradication; and finally, rates of complete overall success, as I defined for you a little earlier, ulcer healing, eradication of H. pylori with no ulcer relapse.

These are the healing rates that we observed after 4 weeks of treatment for the two U.S. placebo controlled studies. Study 305 on the left and 306 on the right. The vertical axis is the percent of patients who

healed and the horizontal axis identifies the treatment groups and the number of patients enrolled.

As you can see, the placebo results were 45 and 15 percent, respectively. The clarithromycin healing results were a bit higher than we expected and were 60 and 49 percent, respectively. The RBC alone healing results were 67 and 66 percent. The RBC plus clarithromycin healing rates were slightly higher and were 69 and 71 percent. These data show both clarithromycin and RBC alone contribute to the healing of duodenal ulcers.

Now, referring you back to the questions that you have been asked to answer today, have the studies shown the efficacy of the treatment regimens for the eradication of H. pylori? This slide shows the observed H. pylori eradication rates in healed patients. The vertical axis is the percent of patients eradicated of the infection, and the horizontal axis identifies the treatment groups and the number of patients in each of those treatment groups.

As you can see, in the placebo and RBC alone groups, 0 percent of the patients were eradicated of the infection. In the clarithromycin group, 36 and 24 percent of the patients were eradicated of the infection. These data show the clarithromycin component of the treatment regimen does contribute to the eradication of the

infection.

Now, what has me most excited about combining RBC and clarithromycin is the impressive eradication rates that we have observed. The combination of RBC and clarithromycin eradicated the infection from 82 and 86 percent of the healed patients, respectively. We believe that these data show a very definite synergy between clarithromycin and RBC in the eradication of H. pylori. Now, these clinical data confirm the in vitro synergy data between RBC and clarithromycin that was just shown to you by Dr. Russell Williamson.

Now, the focus of our studies was to achieve ulcer healing and prevent recurrence through eradication. Now, one of the features of this type of study design is that at the end of the treatment period unhealed patients are considered treatment failures and need rescue therapy. These patients were administered commercially available rescue therapy, and as a consequence, these patients are not available 1 month later to assess for H. pylori eradication.

However, to further evaluate treatment comparisons of eradication rates, we assigned an H. pylori status at the 1-month visit to these unhealed patients and combined with those from the healed patients. These

methods have allowed us to analyze the all-randomized patient population for the eradication of H. pylori. These assigned H. pylori eradication rates are discussed in detail in your briefing document, and I will only summarize them for you here.

Now, this slide shows the range of eradication rates with unhealed patients included. That is from the worst to the best case scenario for studies 305 and 306. As you can see, the rates vary based on the methods used, but even in the worst case, where all unhealed, dropped, lost-to-follow-up patients are considered not eradicated of the infection, RBC plus clarithromycin is statistically superior to all other treatment groups for the eradication of H. pylori.

Now, this slide shows the observed H. pylori eradication rates for the two non-U.S. studies conducted. That is studies T09 and T11. Now, please note that study T11 used the same diagnostic tests as the U.S. studies. Study T09 used the CLO test and the urea breath test to determine eradication. Again, the vertical axis is the percent of patients eradicated. The horizontal axis identifies the number of patients and the treatment regimens.

As you can see, the study on the left, T09, we

observed 94 and 84 percent eradication rates. The study on the right, we showed 81 and 78 percent eradication rates. These numbers are consistent with what we observed in the U.S. studies.

Now, as discussed earlier, we used the same method of assigning H. pylori status to unhealed patients to evaluate all randomized patients. In the worst case, where all unhealed, lost-to-follow-up patients are considered not eradicated of the infection, those eradication rates range from 57 to 71 percent for RBC plus clarithromycin. In all cases, RBC plus clarithromycin was statistically superior to the RBC-alone treatment arm.

A question that may come to your mind is, why didn't you simply use ranitidine plus an antibiotic for the treatment of H. pylori? You might also ask, why didn't you just simply look at a bismuth salt plus an antibiotic, and are these regimens effective against H. pylori?

We did, in fact, look at these regimens. We conducted several studies in which we combined ranitidine plus clarithromycin to assess the efficacy against H. pylori. We did not do any studies using a bismuth salt plus clarithromycin, but we did perform a search of the literature and here is what we found.

Now, this slide is a summary of the efficacy of

equivalent doses of ranitidine, various bismuth salts, and RBC plus clarithromycin against H. pylori. Now, the first line identifies four studies that evaluated ranitidine 150 milligrams b.i.d. plus clarithromycin up to 2 grams per day. Now, two of these studies were conducted by Glaxo Wellcome and they reported a mean eradication rate of 66 percent.

Now, the next line identifies the results from four studies that were published in the literature and assessed the efficacy of various bismuth salts plus clarithromycin and resulted in an H. pylori eradication rate, a mean of 67 percent.

Now, as a comparison, on the third line I have showed a summary of the four RBC plus clarithromycin NDA studies which have employed much more stringent study criteria and resulted in a mean eradication rate of 88 percent. We concluded that ranitidine plus clarithromycin and bismuth plus clarithromycin regimens have some efficacy against H. pylori but are inferior to RBC plus clarithromycin.

Now, let's turn our attention to the overall success endpoints and let's refer back to the questions that you have been asked to answer today. Have the studies shown efficacy for overall success? I will now show you

the data for our primary endpoint, complete overall success. We defined completed overall success, as I said earlier, ulcer healing, eradication, with no ulcer recurrence.

Now, this is a difficult slide. I am going to spend a few minutes making some comments here. This slide shows the life table estimates of complete overall success for study 305. The vertical axis represents the percent of patients who are ulcer free. The horizontal axis identifies the study weeks. On the far left-hand side you will see is the 4-week treatment period, and then the right side is the 24-week follow-up period.

Now, all patients start out here having an ulcer; 0 percent of patients are free of an ulcer. They are then treated for 4 weeks, and as I have noted on the graph, there are two points of overall success that are noted in your questions. This first point here is the proportion of patients who are healed and eradicated of H. pylori, and it is located here right at the 4-week post-treatment visit. Now, the second overall success endpoint, located here at the 24-week time period, is the proportion of patients who are healed, eradicated of the infection, with no ulcer relapse.

Now, the top yellow line here is RBC plus

clarithromycin, as compared to the bottom three lines which are clarithromycin alone, RBC alone, and placebo. Now, for all time points, including both overall success endpoints, RBC plus clarithromycin is statistically superior to all other treatments through week 24 of the study.

Now, this next slide shows the complete overall success results from study 306. Again, I have noted the two overall success time points for you at week 4 and 24 post treatment. What you see is a very similar pattern to the previous study. The top yellow line is RBC plus clarithromycin. The bottom three lines represent clarithromycin alone, RBC alone, and placebo. For all time points, including both overall success endpoints, RBC plus clarithromycin is statistically superior to all other treatment groups through week 24 of the study period.

Now, we assumed the Mantel-Haenszel life table test would be the primary method of analyzing complete overall success since this method enables the use of data for multiple endoscopies performed throughout the study. This method also allows dropout patients to contribute to the analyses for the duration in which they participate in the studies.

However, in an effort to show treatment differences are not restricted to a single type of

analysis, we also prospectively defined two other types of analyses, that is, a crude and modified crude analysis method. These results are detailed for you in your briefing document and will not be presented here.

Now, we conclude that these studies have demonstrated the effectiveness of the combined regimen of RBC plus clarithromycin in patients with H. pylori associated duodenal ulcer disease.

We have also shown that RBC plus clarithromycin has significantly higher complete overall success rates as compared to RBC alone, clarithromycin alone, and placebo.

We also conclude that we have demonstrated the relative contributions of each of the treatment components, RBC alone and the antibiotic alone, to the claimed effects of eradication and complete overall success.

Now I would like to present to you the efficacy results for the ranitidine bismuth citrate co-prescription program with amoxicillin.

Now, as Dr. Gustafson noted a little earlier, this regimen was developed as an alternative for patients whose infections may be resistant to macrolides or who may be allergic to or unable to tolerate macrolide therapy.

This slide shows the patient disposition. The first line identifies the four studies. There were between

98 and 264 active duodenal ulcer patients enrolled in each study. The second line identifies the number of patients who had valid H. pylori tests performed and were confirmed H. pylori infected at pre-study. The remaining three lines identify the number of patients who healed, entered the 6-month follow-up period, and completed the 6-month follow-up period for each of those four studies.

Now, we assessed patient demographics in the two U.S. studies and we found no significant difference between treatments with regard to gender, age, race, tobacco use, or ulcer history.

As I showed you a little earlier, we also measured study drug compliance, and we found patients are very compliant in taking this regimen. Over 82 percent of the patients were at least 80 percent compliant in taking their medication.

Now I will present to you the efficacy data. I will use the same format as earlier, showing you the healing data first, eradication data, and then complete overall success.

This slide shows the 4-week ulcer healing rates for the two U.S. studies, study 303 on the left, 304 on the right; vertical axis, percent of patients healed, and the horizontal axis identifies the treatment groups. As you

can see, 4-week placebo heal rates were between 28 and 20 percent. The amoxicillin healing rates were lower than seen with clarithromycin and with 39 and 55 percent. The RBC-containing regimens had healing rates between 63 and 73 percent. These data were expected and consistent with the data we observed in our RBC plus clarithromycin program. In addition, these data also show the contribution of the RBC component to the healing of duodenal ulcers.

Now, this slide shows the observed eradication rates in healed ulcer patients in the two U.S. studies. As you can see, placebo, amoxicillin, and RBC did not eradicate the infection, whereas RBC plus amoxicillin eradicated the infection in 41 and 48 percent of the patients. Although these rates were not as impressive as with clarithromycin, we observed a very definite synergy between RBC and amoxicillin in the eradication of H. pylori.

Now, as I indicated earlier, since we did not assess H. pylori eradication in unhealed patients, we assigned an H. pylori status to these patients by a variety of methods that have been outlined in your briefing document. These methods have allowed us to analyze the all-randomized patient population for eradication of H. pylori.

Here is the summary. This slide shows the range of eradication rates that includes unhealed patients from the worst to the best case scenario. The RBC plus amoxicillin eradication rates range from 21 to 56 percent. For all methods used, RBC plus amoxicillin was superior to all treatment groups at p less than .42 except for one comparison at .077.

Now, this slide shows the observed eradication rates in healed patients for the two non-U.S. studies, T08 and T10. The study on the left used the CLO test and the UBT to determine eradication of the infection. The study on the right, T10, used the same diagnostic test as the U.S. studies, the CLO test, and histology.

Now, the eradication rates for RBC plus amoxicillin treatment groups ranged from between 46 and 73 percent. We were quite pleased with these results, particularly in how consistent they were with the U.S. studies.

Now, as I discussed earlier for the U.S. studies, the same method of assigning an H. pylori status to the unhealed patients was performed. In the worst case where all unhealed patients were considered not eradicated of the infection, the eradication rates for the four RBC plus amoxicillin groups were between 37 and 59 percent.

For all comparisons, the RBC plus amoxicillin treatment groups were statistically superior to the RBC-alone group.

Now, as I showed you earlier for clarithromycin, the efficacy for ranitidine plus amoxicillin or bismuth salts plus amoxicillin was also investigated. This slide is a summary of the efficacy of equivalent doses of ranitidine, various bismuth salts, and RBC plus amoxicillin against H. pylori.

Now, the first line shows the results of three studies that evaluated the efficacy of ranitidine 150 b.i.d. plus amoxicillin. Two of these studies were conducted by Glaxo Wellcome. They reported a mean eradication rate of 32 percent.

The second line is a summary of 19 studies published in the literature that assess the efficacy of various bismuth salts plus amoxicillin against H. pylori and reported a mean eradication rate of 45 percent.

By way of comparison, on the third line I have summarized the four Glaxo Wellcome RBC/amoxicillin NDA studies, and they employed much more stringent criteria and resulted in a mean eradication rate of 53 percent.

Therefore, we concluded that ranitidine plus amoxicillin or bismuth salts alone plus amoxicillin has some efficacy against H. pylori but is less effective than

RBC plus the antibiotic and did not warrant further development.

Now I would like to move on to overall success for RBC plus amoxicillin. Again, I would like to refer you to the questions that you have been asked to answer today. Have these studies shown the efficacy of the treatment regimen for overall success?

This slide shows the complete overall success rates by life table estimates for study 303. The vertical axis, as I talked earlier, is the percent of patients who are ulcer free; the horizontal axis, the weeks post treatment, and again I have noted the two overall success endpoints for you at the 4-week post-treatment and the 24-week post-treatment period.

For all time points, in comparing the yellow line, RBC plus amoxicillin compared to the other three treatment groups, those intervals were statistically significant for all other treatment groups through week 24 of the study.

Now, this next slide represents the complete overall success rates for the second U.S. study. We see very similar results to the previous slide. Again, I have noted the two overall success time points for you. The top yellow line represents RBC plus amoxicillin, and these data

show RBC plus amoxicillin is significantly superior to all other treatment groups through the 24-week time period.

We also performed two additional analyses of these data using crude and modified crude methods. These results are detailed for you in your briefing document.

Now, we conclude that these studies have demonstrated the effectiveness of RBC plus amoxicillin in patients with H. pylori associated duodenal ulcer disease. We have also shown that RBC plus amoxicillin has significantly higher eradication rates. We have also concluded that RBC plus amoxicillin has significantly higher complete overall success rates than the treatment components. In addition, we conclude that the relative contributions of each therapy component -- that is, RBC alone and amoxicillin alone -- to the claimed effects of eradication and complete overall success have been demonstrated.

Finally, what overall conclusions can be drawn from the data in this clinical program?

Members of the committee, based on the studies that we have presented to you today, RBC, when used in conjunction with clarithromycin or amoxicillin is effective in patients with H. pylori associated duodenal ulcer disease. These regimens significantly improve H. pylori

eradication rates. We have observed up to 94 percent with RBC and clarithromycin. These regimens also significantly improve complete overall success rates in this same patient population.

Thank you for your attention.

It is my pleasure now to introduce Dr. Duane Webb, who is the International Director of Gastroenterology, who will present the safety profile for RBC.

DR. WEBB: Thank you, Dr. Ciociola.

In the interest of time, I will try to move through these slides and perhaps skip through them a bit since you do have the complete set in your handouts and the subject of RBC and antibiotic safety is dealt with quite well in your briefing document.

We feel that RBC has been studied extensively in our clinical trials. The total enrollment in these worldwide trials was over 10,000 patients, we believe one of the largest ulcer programs ever done. Of these 10,000, 5,600 did receive active treatment with ranitidine bismuth citrate at varying doses with and without antibiotics.

The AE profile was similar to that for ranitidine and placebo, and I think that is probably the take-home message of the entire talk on safety. The most

common adverse events we saw were headache, dizziness, arthralgia, occasional nausea/vomiting, diarrhea, darkening stool, which is known to occur with bismuth compounds, constipation, and taste disturbance discussed today in relation to clarithromycin.

We saw no clinically significant drug interactions or bismuth elevation/toxicity. We concluded that RBC plus clarithromycin or amoxicillin was well tolerated in the 2-week co-dosing.

I wanted to point out the overall extent of exposure by treatment group. The majority of these patients were in the monotherapy program for RBC at doses up to 1,600 milligrams per day, and then antibiotic combination programs enrolled a total of around 694 patients worldwide, and a number of patients of course on placebo and the antibiotics alone in these trials. The additional numbers of patients were on bismuth citrate and also on ranitidine in comparator arms in the monotherapy trials.

These overall 5,600 patients were distributed between the volunteer studies and the repeat dose multicenter trials in patients.

I wanted to put into context the content of bismuth that is in ranitidine bismuth citrate in relation

to other bismuth compounds that are commonly in use. In Europe there is a compound that goes by the name of DeNol. Also you have seen it referred to as colloidal bismuth citrate which has, in relation to RBC, a little bit less per tablet. The total recommended daily dose of elemental bismuth is considerably higher. It is used frequently on a q.i.d. basis, whereas the RBC tablet is a b.i.d. dosing with 256 milligrams of elemental bismuth for total daily dose.

Pepto Bismol, OTC in this country, has a total daily dose by comparison of over 1,208 milligrams for the total daily 2 tablets four times a day, and as you well know, this compound has extensive safety record. When they were here for approval for traveller's diarrhea, they quoted 9 billion doses prescribed since 1908 with an excellent safety profile. Most of the difficulties Pepto Bismol ran into were in relation to salicylism in children who had overdosed.

The overall exposure in our single-center studies was up to 2,000 milligrams of single doses, repeat daily doses of up to 1,600 milligrams for up to 12 weeks, and we have conducted long-term dosing studies to be assured of the safety of this compound for up to 1 year, although we are only looking at this for very short-term

therapy of up to 4 weeks.

The pharmacology of this compound I would like to review very briefly. RBC basically has the same drug interactions as ranitidine for the ranitidine moiety of RBC. In antacid co-dosing studies, we found that RBC reduced the ranitidine and bismuth levels by co-dosing with antacids.

We also found that RBC with clarithromycin co-dosing increased the 14-hydroxy metabolite of clarithromycin approximately 30 percent. This was not seen to be of any clinical significance in these studies.

We also found that dosing RBC with food increased the suppression activity of RBC probably due to a delayed gastric emptying and a local effect.

The bismuth absorption of this compound is very minimal, less than 1 percent. In fact, the exact average figure is 0.2 percent of the total oral dose. So, this is really a topically acting activity for the bismuth moiety.

We did measure bismuth concentrations on a systemic level in these patients to be assured that we were seeing no safety problems and to fully understand the bismuth kinetics in these large patient trials. Over 2,700 patients had bismuth assays done during the clinical trials for trough plasma bismuth concentration.

We saw minimal elevations even in the dosing studies that went out to 1 year, and I will show you that data.

In the historical literature on bismuth, there is a key paper by Dr. Hillemand looking at what levels were considered to be of some clinical concern in the history of bismuth exposure, and he had found that a blood level of 100 nanograms per ml was the level at which there was some clinical concern about possible toxicity. We measured plasma bismuth which converts to 160 nanograms per ml. No patients in our overall studies had any levels above 160.

I will show you the dose ranging results in some of our dose ranging trials comparing 200, 400, and 800 milligrams of RBC alone, and we are seeing here levels of bismuth very minimal on a median basis, 1.4 to 3.3, with a 95 percentile range as high as 15. There are always outliers in these types of trials, as we have been asked to comment on, and 1 patient at the 800 milligram b.i.d. dose, a total of 1,600 milligrams, did have a maximum value of 159 nanograms, but there was no associated adverse event in these patients.

The long-term dosing trial was done, as I said, to assess bismuth kinetics over this period of time even for the small amount that is absorbed, and we found that

even over a 12-month period, we saw median bismuth levels far below 5 nanograms per ml with some variation spread, but the highest values seen in these studies were of the order of 40 nanograms per ml, once again far below the historical threshold that had been established in the literature.

There were no serious adverse events associated with this clinical trial. There was 1 patient early in the trial who suffered a myocardial infarction, 47 years old, after a short period of dosing, 1 to 2 weeks. He had a prior history of MI at age 47 and had a cardiac arrest which was considered not related to study medication.

Of the overall adverse events seen with plasma bismuth levels, we saw there was no relation to the bismuth level particularly and the dose of RBC that was given. The ones that were considered either possibly or probably related to the medication were nausea and vaginitis, and the vaginitis situation was attributable to the clarithromycin in the investigator's opinion.

The overall incidence of adverse events in the monotherapy trials is shown here, and we saw the highest incidence of adverse events in the placebo group and the explanation for this is that these patients had ulcer symptoms, they were on placebo, had active ulcers, and they

reported the highest incidence of adverse events. The take-away message is that there were no real differences between RBC alone or the higher doses of RBC compared to ranitidine.

I am showing here the actual incidence of adverse events by event, the highest being headache in the placebo group, but no real differences seen across.

I would like to skip through some of these, if you do not mind.

The co-prescription with antibiotic adverse events, similar profile, highest in the placebo group, a little bit higher in the RBC/clarithromycin group, and that is the adverse events themselves seen here. We did see taste disturbance in these trials and some increase in the diarrhea and GI side effects that one might expect with the antibiotic co-prescription.

Let me skip through some of these since they are in your document.

I did want to show you the drug-related adverse events by treatment arm showing that the RBC plus clarithromycin had the highest incidence of overall adverse events by daily dose of any treatment group. The reason for that was basically that we were seeing problems with GI side effects as a result of antibiotics and the taste

disturbance or taste perversion that was mentioned this morning, a well-known side effect of clarithromycin.

I did want to comment on the deaths that occurred during these trials. On a database of 10,000 patients or more, we had 8 who died during the study. None of these deaths was considered related to study drug. Four of these patients were on RBC, and you see the cause of death: pulmonary embolus, drowning, MI, and sepsis. Three of them were on ranitidine, and these causes were MI, carcinoma, and asthma, and 1 patient on placebo died from carcinoma.

We filed three clinical IND safety reports during the course of these studies, both related to European events and U.S. events. There was one life-threatening allergic reaction to RBC and clarithromycin in a patient who was already known to be allergic to erythromycin. The connection between erythromycin and clarithromycin allergy was not made at that time, but the event was attributed to clarithromycin allergy.

There was one patient hospitalized, actually in the ER, not completely admitted to the hospital, with an allergic reaction of rash to RBC, and one patient in Europe had a hospitalization for unusual behavior which was considered to be related to his previous psychiatric

history, had been on RBC for a short time in a gastritis trial.

Overall the clinical laboratory tests showed no differences across any treatment group with regards to electrolytes, renal, hepatic, or hematology.

I did want to show the experience with pregnancy. Dr. Prizont, our reviewer, had commented on the experience that is seen. The patients were instructed to be on adequate birth control pills or other methods during the trials. However, as in any trial, patients will become pregnant, and I have shown you the experience here.

There was one patient with a pregnancy who did develop a neonate with a sixth finger on one hand. It was thought by the investigator not to be related to study drug but background incidence, and we have some literature search available for you today if there is more discussion about that.

In addition, there was one abnormal pregnancy course in a patient who became pregnant far after the actual administration 3 months after the last dose of RBC, but a normal neonate was delivered despite hyperemesis, gravidarum, and a vaginal hemorrhage.

The other three pregnancies were of normal character, and there was one voluntary abortion.

We did evaluate the safety database with regard to certain special populations as you see here. There were no abnormalities detected in the elderly that would suggest any dosing alterations are required, nor for hepatic impairment, defined as elevated liver enzymes.

In the case of renal impairment, since the primary excretion route of both ranitidine and bismuth is renal, we, from the basis of our clinical pharmacology studies, believe that the drug should not be used in those with severe renal impairment which we define in this case as less than 25 ml per minute creatinine clearance.

As I mentioned, the drug is not recommended for use in pregnancy, and we do not also think it should be used in those who are nursing because it does appear in breast milk.

The pediatric population experience is so limited that we cannot make any recommendations at this time.

The overall conclusion then is that RBC has been extensively used and exposed in patients with an AE profile very equivalent to that of ranitidine and placebo. We saw no clinically significant drug-drug interactions that would cause us to be concerned. RBC plus clarithromycin or amoxicillin was safe and well tolerated

in the co-dosing prescription regimens.

Thank you.

I would now like to invite Dr. Walter Peterson to address the risk-benefit ratio.

DR. PETERSON: I have been asked to make some very brief comments from the perspective of an investigator and a clinician.

The broad question that we want to answer is, why should RBC or any drug plus antibiotics to treat H. pylori be approved by the FDA?

It is well accepted that the eradication of H. pylori leads to a reduced risk of peptic ulcer disease. I think we have all bought into that concept. The NIH Consensus Panel recommended treatment with antibiotics with an anti-secretory agent upon first presentation of H. pylori associated peptic ulcer disease or recurrence.

More specifically concerning the regimens that have been brought before you today, what are the benefits of the RBC plus antibiotic regimen?

Well, we have heard that RBC plus clarithromycin or amoxicillin has been shown to effectively treat patients with H. pylori associated duodenal ulcer disease when looked at in terms of increased overall success, defined as ulcer healing, eradication of H.

pylori, and no ulcer recurrence.

We have heard that RBC may -- and I stress "may" -- and these are in vitro data -- reduce the emergence of antibacterial resistant strains of H. pylori.

We have been told that RBC has been shown to be safe and well tolerated in the patient population studied.

And the regimen is simple, 5 to 6 pills per day.

Now, no antibiotic regimen or no medication regimen is without some sort of potential risks. For that reason, RBC would not be recommended for children, pregnant women, or patients with renal impairment, and there remains the potential for pseudomembranous colitis with use of any antibacterial agent, although in these studies none was found.

So, at the end of the day, what we have here are simple regimens that produce cure of duodenal ulcer disease in a substantial proportion of patients who were so afflicted, and it is safe.

As a final comment, those of you who know me, remember that early on in this H. pylori saga, I was less than enthusiastic about this. I thought that Barry Marshall was out of his mind. I was wrong.

(Laughter.)

DR. PETERSON: I was skeptical, to be honest with you, about ranitidine bismuth citrate, and I was wrong about that too.

Will better regimens be developed? Probably. Maybe. We will not know that until the proper studies are done and the data are brought before you as the appropriate panel for your scrutiny.

Thank you very much.

DR. WEBB: Just to conclude with a few remarks so we can get on to the discussion. You have heard a very nice report I believe today by a number of people who have described the overall clinical efficacy and safety of RBC in conjunction with antibiotics. We believe the data are compelling.

We will be glad to take your questions at this time. We will be able to refer questions to our consultants who are here as well. We have Dr. David Graham, Dr. Barry Marshall, Dr. Pete Peterson, and the Glaxo staff, both from the U.K. and the U.S. who were involved in the clinical trials and specifics, will field your questions.

Perhaps, Rosemarie and Dr. Craig, it would be appropriate at this time to show what we think might be the most appropriate labeling in relation to the discussion

this morning. I have that on an overhead if you would like to take that at this time.

DR. CRAIG: That would be fine.

DR. WEBB: I believe it reflects very much the discussion this morning as to how the labeling could be worded in this case for the clarithromycin co-prescription. "Tritec, in combination with clarithromycin, is indicated for the treatment of H. pylori infected patients with active duodenal ulcer disease. This regimen has been shown to eradicate H. pylori infection to reduce duodenal ulcer recurrences." I believe I have the grammar on that correct at this point.

But I would like to invite Dr. Ciociola also to join me at the podium to help with the questions that you may have since Dr. Ciociola is closest to the efficacy data.

DR. CRAIG: Questions from the committee members? Dr. Judson.

DR. JUDSON: In trying to understand better the relative efficacy of Tritec with amoxicillin versus clarithromycin, was I correct that the overall impression is that the amoxicillin combination is just about half as effective as the clarithromycin both in terms of eradication and in overall success rate at 6 months?

What I took away was that it was something like 25 percent for the amoxicillin combination, about 50 percent for the clarithromycin. I gather most of that was due to the differences in eradication rates. Is that correct?

DR. CIOCIOLA: Yes, that is correct.

DR. JUDSON: And that amoxicillin alone really did not do much.

DR. CIOCIOLA: That is also correct.

DR. JUDSON: Thank you.

DR. CRAIG: Dr. Fisher?

DR. FISHER: Duane, I noticed on your overhead that you put up that you only said the combination with clarithromycin. Does that mean that we should be --

DR. WEBB: Oh, no.

(Laughter.)

DR. WEBB: The very same wording does apply to the amoxicillin co-prescription.

DR. FISHER: Okay, thank you.

DR. CRAIG: Other questions? Yes, Dr. Butt?

DR. BUTT: I was surprised at the low incidence of diarrhea in the amoxicillin-treated patients. It is amazingly low. Do you have any speculation as to why that is?

DR. WEBB: In the antibiotic co-prescription trials, we administered this with food, and we seemed to have a better tolerance of the antibiotic when given with meals. This was a q.i.d regimen. But that is really what we saw. I don't have any other explanation beyond that.

We did not see anything that was really indicating pseudomembranous colitis either. I mentioned that. Although some people seemed to have a possible prodrome to that.

DR. CRAIG: Dr. Norden.

DR. NORDEN: I want to be clear. You found no resistant strains, is that correct, in the post treatment, RBC plus clarithro? That is what is stated in your --

DR. WEBB: Right. That is correct, yes.

DR. CRAIG: Dr. Bertino?

DR. BERTINO: Dr. Ciociola, when you presented your data, you said you looked at a number of demographic characteristics in the amox studies and in the clarithro studies and there was no difference you mentioned in sex, gender.

But in the information that we received -- and it is on page 85 of the blue booklet that we received -- you talk about a greater proportion of male patients with H. pylori infection negative than female patients. This is

in 303 and 304 which was the amoxicillin studies. You then go on to speculate that maybe it is because more men than women had H. pylori at pre-study.

I guess I would be interested in knowing any other data in terms of analysis by sex. I guess that is a possibility but maybe there are other possibilities too why women seemed to have less eradication than men.

DR. CIOCIOLA: We found that to be very interesting also. For those of you, we saw about a 6 to 8 percent higher eradication rate in males as opposed to females.

I think one of the major reasons was that, as I showed you -- I did not show this data, but it is in your briefing document -- 75 percent of the patients enrolled in our studies were males. It appears to be a disease that is predominated by males. So, we felt that may have some suggestion as to why we are seeing a difference in those rates. I have no other reason to suggest why there might be a difference between males and females.

DR. FISHER: It may actually be more just related to your enrollment numbers and criteria as to why there were more men than women, not specifically that the disease is more prevalent in men than in women.

DR. CRAIG: Yes, Dr. Reller.

DR. RELLER: If resistance was not seen to emerge after therapy, especially with the combination including clarithromycin, why did these patients fail?

DR. CIOCIOLA: Russell, would you like to clarify that? I think it is important to clarify that the resistance data that Russell showed was the in vitro data.

DR. NORDEN: I think it is on page 37 -- I just put it back -- of your briefing book, there is a statement that no resistant organisms were found from the group with RBC plus clarithromycin. That is fine. I just want to be sure about that.

Then I would echo Barth's question. Were there failures in that group and why?

DR. WILLIAMSON: Within the group of patients who were enrolled in the RBC/clarithromycin arm, for those patients who we had pre-treatment susceptibility data on them, there was no evidence of resistant organisms enrolled in that particular arm. Therefore, we cannot comment upon outcome with those organisms. We have no evidence that there were resistant organisms enrolled in that patient group.

DR. CRAIG: You state on the second page, though, when you are talking about on 37, that there were 17 patients who demonstrated H. pylori infection resistant

to clari -- this is in the post data -- if one uses zone size and not MIC. Were those MICs sort of in this never-never land that we talked about this morning that we made into a broad intermediate zone?

DR. WILLIAMSON: It is my understanding that all the organisms that were resistant in that group had been treated with clarithromycin alone.

DR. CRAIG: It says 13 of the 20, or 65 percent.

DR. WILLIAMSON: 65 percent, absolutely right.

From the zone diameters, all the ones that were resistant had close contact with the 8-millimeter disk, whereas all the susceptible ones, I think the minimum diameter was something like 45 millimeters and up.

In terms of MIC data, all of those had MICs greater or equal to 0.5 micrograms per ml.

DR. CRAIG: So, in that intermediate zone then.

DR. WILLIAMSON: In that intermediate zone.

DR. CRAIG: Could you also pull up your slide number 12 from the microbiology presentation which was the one in which you looked at the emergence of resistance?

My looking at that for clarithromycin actually looks like for one of the strains it was less likely to develop resistance for the control than it was for the drug

and that for the other organism, you found no statistical difference. So, I did not see any data suggesting that in the in vitro that clarithromycin did it or that your compound reduced the emergence of resistance for clarithromycin.

DR. WILLIAMSON: Yes. With strain 8073, the rate of resistance acquisition was decreased eight-fold by preexposure to RBC in comparison with the control. With the strain 8091, the differences were insignificant between the pre-growth with RBC and the control.

DR. CRAIG: But the way I look at those numbers, it is actually eight-fold the other way around. It looks like to me it takes a larger number of organisms to get one resistant one for the control than it does for the RBC.

DR. WILLIAMSON: I do apologize if there has been a mistake on the slide, but it is my understanding from the experimentation that the pre-growth of this organism with RBC did actually diminish the emergence of resistance.

DR. CRAIG: Okay, it may be a mistake there, but at least the way the slide is and our data books, it does not show a difference.

Could I also look at slide number 31 among the

efficacy study? It is on page 14 of the handout. I guess the question I want to ask -- that is looking at your estimates for eradication using the worst scenario and the best scenario. The question I specifically had is if you had the worst distribution of all so that all of your failures, the ones that did not heal in the combined group, did not eliminate the organism, but all the failures, when you used clarithromycin by itself, did have the organism eliminated, would those differences from the worst in one to the best with clari still be significantly different? In other words, would 44 and 51 percent still be less than the 27 to 30 percent if clarithromycin happened to be the best?

DR. CIOCIOLA: We did not do that analysis.

DR. CRAIG: Yes.

DR. COMER: I have a question. I guess it is really for the statistician. In the agency's handout, it sort of goes through each study in terms of how many you start with and how many end up. In the Glaxo Wellcome thing on page 13, you see that at the end, when they are looking at eradication rates in healed patients, that it is only 13 out of 17 patients. I wonder if there is sufficient power. Are these numbers adequate to make a valid statistical claim?

DR. McSORLEY: Dave McSorley, statistics with Glaxo Wellcome.

The studies were adequately sized, powered for the primary comparisons. However, one of the assumptions that we had was that 95 percent of the patients would be infected with H. pylori. That was reduced somewhat but we still had power to detect statistical differences when we assumed the worst case computed rates for the crude eradication analysis and in the analysis of complete overall success.

DR. COMER: In effect, one-third of almost each study were eliminated because they were Hp negative, and then another third did not heal. So, by the end you are only left with a third of the patients.

DR. McSORLEY: We did not do statistical comparisons in the observed rates for that exact reason. We did comparisons in all the patients where we assigned a status for those unhealed patients so that we would retain all of the patients who were randomized and H. pylori positive.

DR. CRAIG: Yes, Dr. Dunn.

DR. DUNN: There is still a problem of who these patients are representative of at this point because you lose from a third to a half actually of your patients

when you go to those who are Hp positive only. So, the randomization was for the total group. Now you have half.

DR. McSORLEY: Well, randomization still applies to H. pylori positive patients as an a priori subpopulation at entry in the same way as any other demographic characteristic in that since pre-study H. pylori status is a preexisting condition, comparability among the treatment groups is still importantly assured. That was the basis for using the randomized H. pylori patients.

DR. DUNN: With the small sample size, you do not in fact have power to really tell whether they are still balanced with respect to most of your demographic variables.

DR. McSORLEY: Well, for those things that we still had available in terms of data on, the known characteristics, we did do comparisons in that population and showed no differences. We still had power to detect some of those differences because there were enough patients. In terms of the study design power, we actually enrolled slightly over what was originally planned. So, the loss of patients due to not being H. pylori positive versus the over-enrollment to a small extent, we still had sufficient power for those comparisons.

DR. CRAIG: Dr. Judson.

DR. JUDSON: Given that probably the most significant difference that you have shown overall is the one between the efficacy of the regimen with amoxicillin versus clarithromycin, why do you seek an indication for amoxicillin when you have so clearly shown the superiority of clarithromycin?

DR. WEBB: I think the rationale for that is that there need to be alternate regimens in those who are resistant to clarithromycin -- we had one patient with an allergy to macrolides in this case -- to give a clinician something else to work with. As you know, there is no resistance reported to amoxicillin, so we are seeing that.

I think at the last meeting there was a discussion about what minimum eradication rates would be acceptable, and as I understood the discussion, it was one number is simply not enough to make a decision about a regimen. It also involves the resistance rates, the compliance rates, the incidence of side effects.

DR. JUDSON: The indication would be for patients who have already failed once on clarithromycin?

DR. WEBB: No. It would actually read as an alternate regimen for those who are unable to take macrolides or who have strains resistant to macrolides.

DR. CRAIG: Yes.

DR. FISHER: Except that we have not seen any data on the strains that are resistant to macrolides and what happens when you give them the RBC/amoxicillin. Correct?

DR. WEBB: That is correct, but as we said, there is no resistance reported either to bismuth or to amoxicillin.

DR. CRAIG: Do we have any data specifically looking at MIC distributions to see if for those organisms that are resistant to macrolides, their distribution is the same as susceptible strains when we look at amoxicillin MICs?

DR. WILLIAMSON: We find that the clarithromycin-resistant Helicobacter are as susceptible to amoxicillin as the clarithromycin susceptible strains.

DR. CRAIG: Thank you.

DR. MEGRAUD: Excuse me. I can confirm these data. It has been done everywhere and it is true.

DR. CRAIG: Okay, thank you.

Are there any other questions from the committee? Yes, Dr. Temple?

DR. TEMPLE: You did not actually study directly in the same study the question of whether

ranitidine alone would have enhanced eradication rates the same way RBC did. I take it you are asking the committee to consider the other studies done at different times with lower rates of eradication as the basis for concluding that RBC, as opposed to ranitidine itself, makes a contribution. I just want to be clear on that.

DR. WEBB: Yes. Now, that is based on some Glaxo studies as well as our data which we had from Abbott as well. We had worked with Abbott in the clarithromycin co-prescription trials and I think they are here today to comment on that.

My understanding from what they have told us is that if one adds standard-dose ranitidine to clarithromycin, the eradication rate is increased on the order of 5 percent. Does someone from Abbott want to back that up? Carl?

DR. CRAFT: Dr. Craft from Abbott Laboratories.

In fact, 5 percent was the most addition that we ever saw with ranitidine, and sometimes it was essentially just equivalent to clarithromycin alone, depending on the dose. We do know of one study where they went to 900 milligrams of ranitidine a day to increase the levels.

DR. CRAIG: You are referring to eradication.

Am I correct?

DR. CRAFT: Eradication. That is correct.

DR. CRAIG: Thank you.

Dr. Norden?

DR. NORDEN: A last sort of comment and question about the resistance data that you have presented again on page 37. It is troubling that at least 4 of the patients who have resistant isolates to clarithromycin never received clarithromycin and that you do not have the pre-study data, so you do not know what they were before. But it is entirely possible that these are clarithromycin-resistant strains de novo.

That raises a concern already about what kind of population we are dealing with. So, I would sort of be eager to follow up on Dr. Judson's suggestion, which I was going to make, and that is that I think your label for amoxicillin should reflect either clarithromycin failures or clarithromycin-resistant organisms.

DR. WILLIAMSON: To my knowledge, there is no data in the literature that suggests anywhere that the use of amoxicillin either in vitro or in clinical studies actually selects out organisms resistant to clarithromycin. The data is just not there. There is no evidence for that.

DR. NORDEN: I am sorry. That is not what I

said. One of the patients received amoxicillin alone, one received placebo alone, and one received your Tritec alone. So, 2 of the 4 never received any antibiotic but have a post-treatment clarithromycin resistant organism.

DR. WEBB: I think that is a useful suggestion that we will take up as time goes on. I thank you for that.

DR. CRAIG: Dr. Laine.

DR. LAINE: Especially while we have the Abbott representative up there, I was going to ask if there is any more information available anywhere related to the bismuth/clarithromycin combination that there seems to be little information on that you presented. So, I was wondering if Abbott had any more information or you had any more information on that.

DR. WEBB: Right. I understand the question. Carl may have something on that.

DR. CRAFT: We did some early trials with bismuth and clarithromycin and found that it did not add much more than about a 5 to 10 percent increment at any of the doses we used, which included 500 b.i.d. of clarithromycin plus DeNol and doses as high as 500 q.i.d. with DeNol. There was not much additional effect of bismuth subcitrate.

DR. CRAIG: Any other questions?

(No response.)

DR. CRAIG: I think we are ready to move on. We are only five minutes over the hour and a half that was allotted for that period of time. Oh, there was another. Sorry.

DR. COMER: I have a procedural question for the agency. If we approve RBC today for one of these indications, does that mean that we have approved it for duodenal ulcer or are we going to go through this all again at a later date?

DR. CRAIG: Go ahead.

DR. FREDD: RBC alone is a different drug than RBC plus an antibiotic. What you are considering today is a combination drug of RBC used in combination with an antibiotic, and that is the way it has to be labeled. There would not be labeling for the use of RBC alone for duodenal ulcer therapy. It will all be centered around use in conjunction with.

DR. CRAIG: In fact, I think the wording that they suggested at their last time essentially reflected more the eradication and the prevention of recurrence more so than talking specifically about ulcer healing.

DR. COMER: So, we will see this again.

DR. FREDD: You will see what again?

DR. COMER: The GI advisory group will address RBC alone at another time?

DR. FREDD: Maybe yes, maybe no.

DR. CRAIG: Let's move on then to the FDA's medical officer's presentation, Dr. Hopkins.

DR. HOPKINS: Good afternoon. I am Dr. Robert Hopkins. I am a medical officer in the Division of Anti-infective Drug Products. I have reviewed both new drug applications, both 20-558 and 20-559.

In addition, I have had lots of help from a variety of people for both of my applications, including Dr. Dunn sitting over here as a statistical consultant, Dr. Utrup as the microbiology reviewer, as well as many others. In addition, some of my data has been cross-referenced to the other NDA which was reviewed in the Division of Gastrointestinal Drug Products.

I have reviewed essentially eight clinical trials. The four domestic pivotal clinical trials, I have reviewed the primary database. The four foreign supportive trials, I have reviewed summary reports.

The proposed indications have varied over the course of reviewing this application. In fact, they were actually different. The slide that was just shown to you

was a little different than the one that was told to me last week, and so there has been a lot of thinking about exactly how this drug should be indicated, if it should be.

The initial thinking, at least in terms of the study reports and as the application was submitted, was for the treatment of active duodenal ulcer disease and healing and prevention of duodenal ulcer relapse due to a Helicobacter pylori infection when used in conjunction with clarithromycin or amoxicillin.

Then last week -- in your questions actually -- after talking with Dr. Ciociola, he thought this would be a good way to phrase it. It would be, "Tritec, when used in conjunction with amoxicillin or clarithromycin, is indicated for the treatment of Helicobacter pylori associated duodenal ulcers. This therapy has been shown to increase the overall success of treating duodenal ulcers as defined by ulcer healing and eradication of H. pylori infection with no ulcer recurrence." The wording is a little bit different.

The proposed doses again, RBC 400 milligrams combined with amoxicillin 500 milligrams q.i.d -- and RBC, of course, is b.i.d. -- or RBC 400 milligrams b.i.d./clarithromycin 500 milligrams t.i.d.

The domestic pivotal studies essentially were

reviewed. I just wanted to highlight the fact that the patient-to-site ratio was fairly low. Again maybe 3 to 4 patients per site were included in each one of these domestic studies.

In the foreign studies, it increases a bit. Again, what you have really is two ulcer recurrence or overall success studies which are the larger ones, T08 and T09, and then you really have two eradication studies, smaller studies, T10 and T11. They were conducted in a variety of countries throughout the world.

The pivotal domestic studies were placebo-controlled, double-blinded, multicentered. Criteria was consistent with the diagnostic definitions that we set forth in the Points to Consider document. The follow-up was for 6 months. Endoscopy was performed 1 month following treatment, 3 months, and 6 months.

The primary objective, as set forth in the protocol, for all domestic studies was stated as I quote here. "Overall success is determined by the proportion of patients whose ulcer healed during the treatment phase and who remained ulcer free during the 6-month follow-up phase."

The thinking has changed over the course of reviewing the application by the sponsor, and I have

actually done quite a few analyses using this efficacy parameter, which is a purely clinical definition of overall success, although I have done all the other ones also. But just keep in mind, this is how the study was powered.

The supportive foreign studies differed from the domestic studies in that there was no placebo arm.

The RBC 400 milligrams b.i.d. plus antibiotic was the same treatment arm that was used in the domestic studies and, hence, that treatment is supportive.

The clarithromycin dose, however, is different in the foreign studies. It is 250 milligrams q.i.d. as opposed to 500 milligrams t.i.d. Now, that is a lower total daily dose. So, if you show efficacy with this lower total daily dose, maybe that would be considered supportive of the domestic trials which use a higher total daily dose.

In addition, the diagnostic criteria for the two larger recurrent studies, which also assessed eradication, used urea breath test and CLO test. I should mention that the urea breath test has not been approved by the agency yet and that is being recommended at this point to define infection pre-study nor define eradication post treatment.

In addition, looking at the actual way that eradication was defined, it was not the most conservative

approach. If you had a positive urea breath test alone -- I think it is the chart on page 57 in the briefing document -- that patient was considered not assessable. So, it was not a most conservative approach. You might have considered that person positive. So, that might be some of the explanation for why the eradication rates were a little bit higher, and I will describe those further later on.

The other thing is that the eradication studies, T10 and T11, were smaller. They used three tests: UBT, CLO test, and histology. I actually requested that the company recalculate their eradication rates as they have using the CLO test and histology alone to make it consistent with the division's recommendations. So, those rates would be calculated similarly as to the domestic studies, the smaller eradication studies.

Exclusion criteria. I do not want to go through them all. In fact, I pulled most of the slides to try and shorten my talk. I just want to emphasize that the exclusion criteria list was long, and I had four of these slides, but I will relieve you of the need to review them all. It was very long, and probably the only one that is worth mentioning is the NSAIDs. These patients were supposed to not get into the study.

Blinding. The study was very well blinded.

Patients, investigators, pathologists, study personnel, contract staff, Glaxo medical personnel were all blinded to treatment. I should probably say that as I reviewed the primary database, I was also blinded to treatment.

(Laughter.)

DR. HOPKINS: No, I think that is important. That is not a joke actually.

It was a double-dummy, so you used placebo medications. I pulled out some of our blinding slides too, but essentially it was very well blinded. They took great lengths to make sure that the endoscopist was not aware of what medication they might be on, given that bismuth does turn your stool dark, and I will not go into all that, but it was very well blinded.

The compliance. Essentially the patients were given a phone call during the first week of the study, and patients who consumed less than 80 percent of the intended dose were considered noncompliant.

The only catch here is that the intended dose was not actually the dose. I guess the intended dose would be the prescribed dose, but patients were actually given more drug than was intended. So, it complicates exactly how you calculate the compliance rates. If the patient is given, for example, 100 pills and the protocol says you are

only supposed to take 70, what do you do with that patient that took 100? So, the compliance may be 125 percent in a few of these patients, and so it complicates the compliance calculation.

However, most of the patients actually did not take over the amount, and very few, almost none, took greater than 120 percent. When they say compliance was over 80 percent, that is true. It is just that you have to remember they were given more drug than was actually intended.

Ulcer definitions for the infectious disease community probably more than the GI community I will just go through real quick. A break in the mucosa with depth that extends through the muscularis mucosa and is between .5 and 2 millimeters in diameter.

Healed ulcer was very strict in that you required completed re-epithelization of the ulcer with or without erythema.

An ulcer relapse was a break in mucosa of any size with depth that extends through the muscularis mucosa.

The definition of infection pre-study and the definition of eradication post-study. I am not going to take the time to go into this in great detail although I know it is very important and we did not have time to talk

about this at the last advisory committee meeting. But the criteria were developed internally, and basically what we tried to do was maximize the specificity of infection pre-study to make sure you are keeping people who are not infected out of the study and then maximize insensitivity post-study. So, they are fairly strict. I do not think I need to say much more about that.

The only thing I might say is that patients with missing H. pylori status data at the end of treatment were actually by the sponsor considered missing. If they were assessed for eradication at the 4-week time point, they were still considered missing. So, they needed to be defined as eradicated both at the end of treatment and at the 4-week time point.

My definition actually was less strict in that I did not really care what your H. pylori status was if it was missing at the end of treatment. If you were assessed at 4 weeks, then I took that result. So, that is why my eradication numbers may be a little bit higher in some of the studies, not much, than other studies.

Again, if you were positive, if you were infected at the end of treatment, you were considered not eradicated.

Protocol violations. Essentially they defined

three kinds: major, minor, and deviations. Essentially the list of major protocol violations was very similar to the exclusionary criteria, and the minor protocol violations mainly related to safety. I will go into these in detail in a second.

The major protocol violations were long. The only thing I really want to mention is that the main one I think was probably the patients who had less than 80 percent compliance in terms of excluding patients who had major protocol violations. I considered analyses -- and I will describe later -- which took in consideration patients who had major protocol violations either pre-study or during the study at various time points.

The sponsor's patient populations are important to keep in mind. There were essentially three: the intent-to-treat or safety population, and then the microbiologic evaluable population, which was split up into two parts, part 1 and part 2. Part 1 essentially was patients who were infected pre-study, and part 2 was patients who were infected pre-study and also entered into the post-treatment observation phase.

Then, furthermore, they defined retrospectively in the domestic studies, although prospectively in the foreign studies, what they call an efficacy population.

These are patients who had a major protocol violation and they split them up into two parts too. Part 1 would be patients who had a major protocol violation either pre-study who actually got into the study or up to the point of healing. Part 2 would be anyone that had one anywhere along in the study both in the beginning or at the end.

I actually defined three efficacy populations to be more precise I suppose, and those were anyone who had a major protocol violation up to the point of healing as one efficacy population, anyone who had a major protocol violation up to the point of eradication at 4-week follow-up point as another efficacy population, and anyone who had a protocol violation anywhere along in the study as a third efficacy population.

Again, the reason for defining these efficacy populations is to determine what the results are in patients who actually took the medicine the way they were supposed to. So, they are going to be inflated, but it gives you a feeling for what happens if you take the medicine correctly.

The way I reviewed the data was that I essentially initially assessed Hp status and DU status pre-study. Then next what I did was I assessed the disposition of the patient at the 4-week follow-up point. Within that

4-week follow-up point, I considered both healing at the end of treatment and eradication at the 4-week follow-up point. So, what I was able to do is actually classify a patient as either healed and eradicated; healed, not eradicated; not healed and cleared; and not healed and not cleared.

Now, I need to be clear about what clearance is. It was not clear in the previous discussion.

(Laughter.)

DR. HOPKINS: That went over your head.

(Laughter.)

DR. HOPKINS: Basically clearance is defined as H. pylori not present at the end of treatment. So, when you do analyses considering patients who are cleared or not cleared, you need to remember that it is probably a fair assumption to assume that a patient who is not cleared is not eradicated. But the assumption that a person who is cleared is going to go on to be eradicated is probably not a fair assumption. So, I have done a variety of analyses and I will describe them in a second.

In addition, I looked at all the data to validate the sponsor's assessment as to whether the patient recurred up to the point or before any time within the study, 6 months.

In addition, I looked at withdrawal information to make sure and the time when the patient withdrew, so we were able to actually able to assess life table assessments to give patients partial credit for getting further along into the study if they had dropped out.

Then finally, I described these efficacy populations considering patients who had major protocol violations anywhere along in the study, as I previously defined.

One thing that we do at the FDA in the Division of Anti-infective Drug Products is review applications often on a patient-by-patient basis. The sponsor made available to me an electronic submission which allowed me to actually visualize the entire case report form essentially from an individual patient so I could make a clinical assessment and validate their results both clinical and microbiologic. So, I had all the data in front of me as I went through all 800 patients.

I think that is important in that you find -- in addition to the raw data, what they submitted is information such as investigator comments and endoscopy comments. You have information on what medicines they are on, whether they took ranitidine for a symptomatic episode. All this information you have in front of you. So, you

really can get a good flavor for whether that patient is evaluable, whether they actually healed, whether that person should not be considered evaluable.

Once I entered all my data into my own database, I sent it to my statistical consultant who cross-checked the data to the SAS data set that the sponsor sent her, and any differences were either corrected or resolved.

Just as a brief illustrative example, in one patient the patient was classified as missing healed data at the end of treatment and withdrawn during treatment. If you look into the comments that the investigator had, you noted that the patient had not completed treatment because of severe ulcer pain which prompted the patient to go seek emergency care on vacation. So, therefore, I considered that patient to be unhealed at the end of treatment even though that patient was not captured in the data set and was not observed to be unhealed. What do you do with that patient? If you see that, if you observe that information, you can look at the data a little bit differently.

This is an illustrative example. It did not happen that often. Actually most of the differences were in the assessment of eradication, as I described before, where my eradication rates go up actually because missing data are actually carried forward in those patients who are

actually considered eradicated. So, the sponsor definition of eradication was stricter than mine. But you do see differences.

With such low numbers of patients, I think it is very important to be very strict about going through each one of these patients to make sure that the data is valid.

In addition, I asked Dr. Hugo Gallo-Torres in the Division of Gastrointestinal Drug Products to review the endoscopy data and make sure that of those patients who actually had ulcers pre-study, recurrence post study -- he validated all the endoscopy data and he looked at those patients who had greater than four or more procedures. He found a less than 1 percent discrepancy between endoscopic data and the consultant substantiation of coding, suggesting that the endoscopic data, as entered into the database, was fairly complete when you compare that to the endoscopy records the investigators submitted.

One of the things that you need to take home here is that I did 23 analyses. I do not know what the p value is but I think that is significantly lower than what the company has presented. However, I submit to you that it is also -- I mean, significantly higher. Sorry. However, I submit to you that it is significantly lower

than the number that was submitted to me in the NDA. Sometimes I thought there were more analyses than patients.

(Laughter.)

DR. HOPKINS: I am not sure. I did not count them up.

But essentially what I did was I did eight eradication analyses, three ulcer healing analyses, two ulcer recurrence analyses, and then I did overall success analyses totalling 10.

Again, the definitions. I did six of what I call clinical overall success. Pardon the terms if you do not like the term "overall success." But that is defined as ulcer healing and no ulcer recurrence regardless of eradication status.

Then I did three what I call surrogate overall success which is only including ulcer healing and H. pylori eradication. Again, the term probably is not the best one. Essentially that is an eradication analysis considering healed patients in different ways.

Complete overall success. I did one. I did the crude complete overall success.

When you look at ulcer recurrence, you need to be very careful about what you do with your dropouts. The company put forth a variety of methods in treating

dropouts, and I will go over those in a second.

In addition, you need to be very careful about what you do with your protocol violators. Again, what I have done is I have defined varied efficacy populations and then repeated the analysis with a different population. Hence, you get increasing numbers of analyses. But all that does is just tells you what happens to the analysis when you have a very select group of patients who actually take the medicine correctly.

Then finally, I have treated unhealed patients in the eradication analyses different ways and I would like to go into that now.

The crude and the observed are fairly straightforward. I do not think I need to explain that. Again, the reason why they are called crude as opposed to intent-to-treat is because the denominator is all patients who were infected pre-study as opposed to intent-to-treat. The observed is the very select group of patients who actually were observed to be assessed for eradication at 4 weeks. I did not use 3 months.

Then I define some atypical types of analyses. The first one I call "Refined Medical Officer Observed Analyses" because we all know that medical officers are refined. What I did was essentially I made the assumption

that patients who were unhealed and uncleared -- I made the assumption that those patients were not eradicated. In my mind that assumption seems to be valid. However, the assumption that the sponsor makes in their refined observed that they presented was that not only patients who were unhealed and uncleared were not eradicated, but they also suggest that patients who unhealed and cleared were eradicated. Hence, the confusion about clearance.

Then finally, I did another analysis which only considers healed patients. So, unhealed patients are simply not included in the analyses.

This graphic simply demonstrates some of the discussions we had prior to my presentation about what happens to the patients when you take the randomized population here. This is the randomized population in blue diamonds, and the red circle is the patients who were microbiologically evaluable or patients who were infected pre-study. Then the arrowhead here are patients who were observed to be assessed for eradication. So, when you look at the observed eradication rates, you are looking at the population here on the arrowhead.

So, again, as was emphasized earlier, the proportion of patients who were observed to be eradicated -- these are not eradicated, but observed to assessed for

eradication was much lower than the randomized population and much lower than the population who were considered microbiologically evaluable or infected pre-study.

Again, the difference between here and here is for two reasons. One, patients were not infected, and number two, they did not have enough microbiologic criteria to define infections. So, they had missing data, for example.

Then the difference between here and here is patients who dropped out during treatment or during the 4-week follow-up period and patients who had missing data at the eradication time point and also unhealed patients. Again, patients who were unhealed were not assessed for eradication.

So, you have much lower numbers in all treatment arms. In fact, just to give you an idea of the numbers, since placebo does not heal, what you end up with -- you know, the red dot is a little bit farther over here, and you wonder whether this is because they were not healing. And you end up with 3 patients in a couple of these protocols in the placebo arm. So, 3 patients were observed to be assessed for eradication.

This problem really comes up with any analysis that you look at, including a recurrence analysis where you

look at a population after the healed stage.

To describe in more detail what the crude and the modified crude and the life table analyses are, I think you need to understand this to understand what I am going to be describing in a few minutes.

Now, this deals with the analyses that look at clinical recurrence or these would be either clinical overall success, ulcer recurrence, or complete overall success, anything that evaluated recurrence in their definition.

The crude analyses essentially are all microbiologically evaluable patients, and they are all included in the denominator.

The modified crude analyses subtract out patients with unknown healing status, in other words, patients who did not have endoscopy, and subtract out patients who are known to be healed at the time of dropout. In other words, what you are doing is you are taking away patients who you are not sure -- you are just removing them. The patients who dropped out because of recurrence are left in, of course, as failures, but you are removing all the other ones because you do not know what happened to them.

Then finally, the life table or Cutler-Ederer

analysis is much more complicated, and I do not know if I want to read this complex description. But essentially what happens is you are giving patients partial credit on a per-interval basis for getting farther and farther into the study. So, if you get 3 months into the study, you get more credit than if someone gets 1 month into the study.

It is similar to the modified crude analysis in that you subtract out all dropouts with unknown healing status, patients who have no endoscopy. However, the difference is the patients who are known to have healed at the time of dropout. What you do essentially is you add a half a person on a per-interval basis to the numerator and you subtract a half a person from the denominator on a per-interval basis. So, it is a little bit complex but that is what it means.

The methodological differences in the analyses, when you look at the sponsor analyses versus the medical officer's and the statistical officer's analysis, were that the crude analyses that were not presented earlier by the sponsor that I will present were a LOCF analysis. In other words, this is the last observation carried forward. So, if you were healed early and then you dropped out, you were carried forward as a success. So, you need to ask yourself whether that is an appropriate way to analyze the data.

What I have done -- and this is why my crude rates are lower -- I have done a non-LOCF analysis where I assume that these early successes are not early successes.

Finally, when you look at all analyses, whether it is a crude, modified crude, or life table, what the sponsor has done is they have looked at the scheduled visits versus the medical officer which looked at both unscheduled and scheduled visits. So, essentially what I am suggesting is patients who are symptomatic may be more likely to have a recurrence than someone who does not have symptomatic. If someone has an unscheduled visit, they are more likely to be symptomatic -- I mean, it is more likely they have an ulcer recurrence. So, I included both scheduled and unscheduled visits.

The treatment of protocol violators were essentially simple. Again, I repeated the analyses using three different efficacy populations. I described that before.

To get to the results, I am going to first present just the eradication rates for the different types of analyses for the amoxicillin studies just to give you a flavor for what the difference between the sponsor's result and the medical officer's result is and also give you a flavor for what happens when you treat unhealed patients

differently, depending on whether they are cleared or not cleared, et cetera, or if you are only looking at healed patients alone.

Essentially the eradication rates vary from 55 percent to 36 percent. This is higher than the eradication rates reported by the sponsor, 41 percent to 21 percent. I do not like to look at this one because it makes an unfair assumption, but I leave it here for your information. For 304, 55 percent to 39 percent. These other analyses give you a flavor for what happens when you treat unhealed patients differently. Again, they are higher in these two studies for the medical officer than the sponsor.

The clarithromycin studies. Again, for this study you actually get a higher observed eradication rate and you get a little drop-off when you treat unhealed patients differently. When you don't include them, it is 77 percent. Worst case scenario, however, would be 53 percent. Worst case scenario here is 57 percent. In this particular analysis, I get a lower eradication rate for 306 than the sponsor's result.

I just showed this slide again in case you forget what these terms are. But I want to go over the overall success results.

The clinical definition of overall success --

again, I am getting lower numbers, 30 percent to 41 percent, depending on how you do it, life table assessment or crude analysis, versus 47 percent or 48 percent. Now, this is healing and no recurrence. There is no eradication in here.

The surrogate analysis. Essentially it is really a crude eradication analysis. So, the sponsor did not define it but that is what it is. It is essentially the same as I presented before, 36 percent. Again, I am getting a higher result here because all unhealed patients are considered failures. 21 percent for the sponsor.

Then for the complete overall success, again this is a crude crude in terms of not doing a LOCF analysis. I get 21 percent and they get 21 percent. Again, the way I consider eradication probably equaled out when you look at the way the sponsor did the analyses for overall success. So, it really equals out for this protocol, 303.

When you look at 304, rates here of 30 percent, again lower for clinical overall success. Remember, this is how the study was powered, this definition. The sponsor gets higher rates on their non-LOCF crude analysis as well as their modified crude and life table assessments.

When you look at the surrogate analysis, 39

percent -- again, this is really an eradication rate -- versus 30 percent.

In complete overall success, I am getting 14 percent for my crude analysis. I did not do modified crude or life table assessment. And the sponsor is getting 18 percent for their crude analysis.

305. Overall success rates jump up, of course. This is with clarithromycin. Although my numbers go down a little bit when you look at just clinical endpoints, 47 to 58. The sponsor is 56 to 60.

Surrogate analysis. My numbers are up, 53. 44 percent for the sponsor.

And complete overall success, 38 percent. My number is actually higher than the sponsor's, suggesting that the eradication effect probably played into that. That is why my numbers are higher for the complete overall success.

The last study, 37 percent. Again, my numbers are lower for clinical, higher for surrogate, 57 percent, and a little bit higher for complete overall success when you just do the crude as opposed to the sponsor's analysis. Again, the eradication effect probably made the difference as to why you see a difference in complete overall success for that particular study.

What I am going to show you now is sort of a tour of efficacy. I have seven projections for each protocol. Just to give you a feeling for the numbers of patients, I show the 95 percent confidence intervals for each analysis. This analysis is actually eradication in the microbiologically evaluable population. This is the same, although you cannot read it here at the top. This is for 304 and this is for 303.

I should say that these red dots here signify statistical significance, and one of the main take-home points here is that regardless of how you do the analysis in the microbiologically evaluable population, you achieve statistical significance when you compare the RBC plus amoxicillin to any of the comparator regimens. Even though these numbers are small, you are achieving statistical significance, as the sponsor has in their results. Now, the rates are fairly low, but you are getting a difference between the comparator regimens.

When you look at observed, 55 percent, similar rates in 303. Again, this is the analysis, refined medical officer observed, dealing with those uncleared patients. This is the analysis where you only look at healed patients. So, if you only look at healed patients, you are looking at 55 percent similar rates over there on 303.

When you look at the efficacy populations for eradication, the rates go up. I do not want to dwell on this slide because this is not the population that is going to be treated, but if you want to know, if you take the medicine correctly, your rates will go up.

Ulcer healing as presented by the sponsor. You do not see a big difference, as you would expect, between RBC and amoxicillin for any of these two studies, but you do not find any statistical significance except you do, of course, with placebo here. They find a difference.

When you look at ulcer recurrence, you will realize why you don't look at ulcer recurrence. The 95 percent confidence intervals overlap dramatically. Again, you have low numbers, so you are not going to find any statistical difference. But if you do not look at the amoxicillin and placebo, you do see sort of an effect, a numerical effect, of reduced ulcer recurrence, 23 percent versus 58 percent, 38 percent and 70 percent for 303. I do not know if the efficacy population is worth looking at in that analysis.

When you look at the clinical definition of overall success -- again this is how the study was powered -- you do not get any statistical significance in any of these analyses whether you look at a crude crude, which is

what I have done, a modified crude, or a life table assessment. Again, the life table assessment. I am just looking at a cumulative life table assessment in looking at the end of that 6-month time point. Those are the points I want to give you for the clinical.

For what I called the surrogate overall success definition, which is really again a crude eradication rate, you do find statistical significance. Again, this is just a different way of handling unhealed patients. If you assume they are failures, you still find statistical significance regardless of how you do the analysis.

When you look at the crude crude or non-LOCF complete overall success rate, you get very low complete overall success for 304, 14 percent and I think it is 21 percent here for 303. They get a red dot here for RBC, although they do not for amoxicillin or placebo. I don't think they make here on placebo on 303.

Again, the sponsor presented the life table complete overall success rates. So, that is a little bit different way of looking at the data.

Now you have got halfway through it. This is the other half of the tour of efficacy.

This is the clarithromycin efficacy data in combination with RBC, and this is the eradication rates.

Again, you get much higher eradication rates here for clarithromycin. When you look at the crude, 57 percent from my analysis. Again, these are higher than the sponsor's. 83 percent. And you achieve statistical significance across the board in both studies, regardless of how you look at the data, when you look at healed patients only down here or if you assume certain things about the uncleared patients in the observed analysis.

However, I should mention here these were a lot of analyses, and it seems impressive, but these 95 percent confidence intervals are still a little bit concerning. If this is 57 percent, could it be actually 40 percent? So, even though you achieved statistical significance, you still have large 95 percent confidence intervals.

The efficacy population. Again, you increase. Again, in this case it is 94 percent for the observed. Again, I only did the efficacy populations in those least conservative analyses, again reflecting what we call in the Division of Anti-infective Drug Products evaluable analyses, patients who took the medicine correctly, everything was clean. But these do not necessarily represent what actually happens in real life, but the rates are higher and you have statistical significance for each combination therapy compared to the control arms.

Healing data. Similar to the amoxicillin studies. No statistical significance compared to RBC alone for either study. Looking at the efficacy population here probably is not helpful. You get statistical significance for the observed healing rate compared to the combination therapy in 305 -- 306.

Ulcer recurrence. Again, you see a numerical effect although there is no statistical significance here because of the low numbers.

Clinical overall success. Again, there are a few red dots here, but in general you don't make it in terms of comparing the combination therapy to the control arms. And the rates are not real high, 37 percent.

And surrogate. Again, this is essentially the crude eradication analysis. Crude eradication or surrogate overall success, 57 percent. Statistically significant in both analyses, both studies.

Then finally, the crude crude or non-LOCF complete overall success analysis where you find 34 percent versus I think it is 39 percent, if I can read that. You find statistical significance in my analysis when you compare this to RBC. You do not when you compare it to clarithromycin for 306, and you do when you compare it to placebo. You find this again for clarithromycin.

So, the foreign data is much different than the domestic data. However, the eradication rates are very similar. This is the data for the applicable study arm. RBC 400 milligrams b.i.d., amoxicillin 500 milligrams q.i.d., and you are getting similar eradication rates whether you look at a crude or observed. Again, these rates here should be only considered supportive because of the way they defined eradication in the test that they used. So, although they are higher, I do not know whether we can look at them as strongly.

The clarithromycin eradication foreign data represented here, 57 percent and 81 percent eradication whether you look at an observed or crude analysis, again very similar to the domestic studies. Again, I just reviewed the summary reports.

Then finally, overall success if you use a LOCF definition, interestingly, it is much higher. When you compare the clinical definition of overall success, it is 76 percent and 84 percent when you look at the foreign studies as compared to the domestic studies. This is for the amoxicillin and RBC combination.

When you look at the analysis of the association between eradication and reduced ulcer recurrence, the sponsor did this in a variety of ways. I

am going to summarize the simple method which is looking at the association between eradication and ulcer recurrence in terms of looking at only those patients who were observed to be assessed for eradication at the 4-week time point and were followed all the way up to 6 months, and if they recurred, they were included in the analysis. So, this is what I call a primary surrogate analysis.

If you look at the foreign studies, you see an ulcer recurrence rate in Hp negatives of 4 percent versus Hp positives of 42 percent. However, if you compare that to the domestic studies, the recurrence rate of patients after 6 months in the primary analysis was 28 percent versus 57 percent. So, there appears to be a dramatic difference in the surrogate analysis whether you look at the foreign studies versus the domestic studies.

Maybe that is explaining to some extent why you see different overall success rates in the foreign data for the two larger studies when you compare those to the domestic studies. When you include them all together, the data looks pretty good, and this was presented in October.

Again, I am not including any of the studies, the domestic studies, which did not use antibiotics. So, these are all studies which used antibiotics.

If you like numbers --

(Laughter.)

DR. HOPKINS: -- this is it. If you are really going to compare the significance of these analyses, I think you need to look at all the numbers and not just one life table analysis. So, if you want to look at it, you can. However, I am just going to give you general concepts here.

This is the medical officer's statistical comparison. This is the sponsor's statistical comparison. If you look at the clinical overall success rates -- again, this is not complete, which is what the sponsor is now promoting -- for the medical officer the 95 percent confidence intervals of the differences include 0. So, you are not getting statistical significance for the amoxicillin studies and you don't make it for all of the clarithromycin studies. Again, the sponsor has similar types of -- they are doing p values here, but the results are fairly similar.

However, one thing you might notice is that these two foreign studies look good. The clinical overall success rates were very high.

If you look at the surrogate analysis -- again, this is just looking at the crude surrogate analysis and the crude clinical overall success. This essentially is

again the crude eradication rate, and again you get statistical significance. So, if you are going with eradication, whatever you want to call it, you are going to get statistical significance, if you are going with the definition of healing plus eradication, and the numbers are similar here for the sponsor's results.

Now, if you go with the complete overall success rates in terms of comparing regimens, comparing control arms, you do not make it in all study arms for the crude analysis. Again, this is 303. It includes 0 here and 306 includes 0. I am sorry. These two actually should be reversed. This block is 304 and this is 303.

If you look at the complete overall success rates, the crude complete overall success rates -- again, crude is a LOCF crude. You do get some statistical significance when you compare arms for the amoxicillin here and here and here. However, you don't make it for all the clarithromycin arms. There is one that doesn't make it here on the crude. However, again in the life table, as they suggested, their complete overall success life table assessment was statistically significant when you compare all arms.

When you look at the life table analysis of the crude rates -- I am sorry. When you look at complete

overall success and you compare the sponsor's crude rates to the life table analysis, you can see that you get statistical significance across the board. However, when you look at the sponsor's LOCF crude, you don't make it in all study arms. So, it all depends on how you analyze the data.

That's it for efficacy. We got through that one.

The safety I do not want to spend a lot of time on. I just want to mention that, as Dr. Webb suggested, the number of adverse events were very similar to the placebo arm for amoxicillin, clarithromycin, even for the two regimens that used the antibiotic plus the RBC. However, you do get the taste disturbance here, 10 percent in this regimen and I think 11 percent in this regimen.

I just would probably mention that although there are 10,000 patients in the safety database, the patients who actually received the regimen to be marketed was much less. So, if there are any rare side effects in terms of interaction, we might not pick it up.

Then finally, I just want to mention a brief point on the bismuth levels. You do see an interaction here when you look at the median bismuth levels. After 4 weeks in the foreign studies, you have an increase of 5

nanograms per milliliter, and I think the median here is 7 or so. So, you do see a little increase in your bismuth levels when you administer clarithromycin concurrently. However, it is probably not clinically relevant.

Then finally, probably the most important slide I have, although it is not mine -- I stole it from Dr. Linda Utrup, and you will probably see it later. This slide represents the numbers of patients who had any MIC data or disk diffusion data result at any visit. It just deals with clarithromycin. For the study 305 and 306, which included -- for the study arms RBC plus clarithromycin versus just clarithromycin alone monotherapy, you can see that there were no patients who were assessed both pre and post-therapy who had culture and MIC or disk diffusion data. So, we really have no idea whether -- we have no clinical feeling as to whether when you give this medicine to patients whether you may or may not be preventing the development of resistance. We do not even know if it induces resistance. We know nothing because we have no patients.

However, of the patients who actually failed eradication in the observed analysis, there did not appear to be any relationship with lack of compliance. This again was the same with the clarithromycin arm. Very few of the

patients who actually failed were noted to have less than 80 percent compliance.

So, in conclusion, I have a few questions that I would like the committee to help me sort out.

The first question is, what is the appropriate efficacy endpoint or endpoints? It is the same issue that we dealt with in the previous application.

Second, have safety and efficacy been demonstrated?

Third, what are the true H. pylori rates when you consider large 90 percent confidence intervals and the fact that we are not assessing eradication in patients who were unhealed?

Fourth, will emerging resistance to clarithromycin be a problem, given the fact that we have really no clinical data?

Fifth, why is there a difference in the overall success rates and the surrogate analyses in terms of the link between H. pylori eradication and ulcer recurrence when you compare the foreign studies to the domestic studies?

That concludes my talk. Thank you.

DR. CRAIG: I understand Dr. Prizont will not present his -- are you going to present?

DR. PRIZONT: (Inaudible.)

DR. CRAIG: Specifically, I guess are there any quick questions of him someone wants to ask right now, or can we move on and then come back to this in our discussion?

DR. COMER: Excuse me. There are a number of people that are going to be leaving, and I wonder if maybe we should just proceed with the questions.

DR. CRAIG: We have got one more quick presentation yet.

DR. FISHER: Let me just add to that that the California contingency does have to leave. So, from what I understand, Dr. Fanning, you will be contacting that group for their comments by conference call perhaps tomorrow. So, we will say goodbye to our colleagues and proceed and thank them all for coming.

We will proceed with Dr. Utrup.

DR. UTRUP: I would like you to focus on one main issue during my presentation and that is, are there enough microbiological data in these clinical trials that can be correlated with clinical outcome to support establishing breakpoints for the combination of Tritec and clarithromycin or Tritec and amoxicillin?

I will skip over these.

The methodology used is agar dilution MICs. I do have to explain this last one. The MIC ranges tested for amoxicillin were .015 to .125 micrograms per ml, and that for clarithromycin was .015 to .5 micrograms per ml.

With the sponsor's proposed breakpoints of MICs less than or equal to 2 as susceptible, 4 is intermediate, and greater than or equal to 8 as resistant, when you look at the clarithromycin, the highest concentration tested was .05. So, if you had a result that was greater than or equal to .05, you could not possibly determine whether it was susceptible, intermediate, or resistant.

Similarly with the amoxicillin, the susceptible breakpoint was less than or equal to 8 that they used. If you go back here, the highest concentration tested was .125 micrograms per ml. Again, it would be impossible to tell whether it was susceptible, intermediate, or resistant if you had a value of greater than or equal to .125.

I am skipping over all of these because I know everyone has to leave here.

As Dr. Hopkins just said, this is the slide where I am comparing the RBC plus clarithromycin results, and I must say that I was very lenient in including the patients in this chart. I included everybody that had any kind of MIC value whether it was disk diffusion, whether

it was an MIC. I even counted all those that I could not determine what the range was, the greater than .05. I included even those that had discrepancies between disk diffusion and MICs. I did this without regard to ulcers or ulcer healing or anything, and even patients that might have had two values at different points post therapy I included as two patients.

So, as you can see here, pretreatment there were a total of 20 isolates that I had any values on at all. There was one isolate that had a post-treatment value, and the most important thing, there were absolutely no patients that had both pre and post-treatment susceptibility results. So, it would have been impossible in this situation to ascertain whether there was acquisition of resistance because there were absolutely no patients that had these values.

In the monotherapy arm, there were 23 patients with pretreatment values. There were 24 with post-treatment values. There were 6 that had both pre and post-treatment values, 4 of which went from susceptible to resistant; 2 remained susceptible.

The sponsor states, as has already been brought up, in the briefing document that there no resistant strains in the post-treatment group. As you just saw, the

number of susceptibility results in the post-treatment therapy, there was only 1 patient and that patient had an MIC of greater than .5 micrograms per ml. Again, we are not able to say whether that is susceptible, intermediate, or resistant, and there were absolutely no results in both pre and post therapy.

In analyzing the clarithromycin monotherapy arm, the sponsor said that there were 3 patients that acquired resistance. The number of patients that had both pre and post-therapy results was 6, 4 of which in my analysis had acquired resistance.

The analysis of the Tritec and amoxicillin. There were 12 patients that had pretreatment results in the combination, 13 had post-treatment results, and there was 1 patient that had both pre and post-treatment susceptibility testing values.

In the amoxicillin monotherapy, there were 4 patients that had pretreatment values, 16 that had post-treatment values, and 2 that had pre and post-treatment values.

The sponsor has stated that there are no resistant strains in the post-treatment group, but the number of test results post therapy was 13, and the number that had both pre and post-therapy results was 1 patient.

Some of the in vitro data. You might ask yourself what the level of Tritec or clarithromycin was at the site of infection or the combination of the two components. There were no studies done to determine that for RBC or bismuth.

In the MIC data, 19 H. pylori isolates were tested. The RBC arm, the modal MIC was 8 micrograms per ml with a range of 4 to 31 micrograms per ml. With the bismuth arm, the mode was 16 micrograms per ml with a range of 4 to 62 micrograms per ml. Ranitidine was greater than 125. The sponsor says that RBCs have significantly lower MIC values, but the difference between 8 and 16 is within the error of the test and there are also quite large ranges here.

Kill rates were also assessed. Three H. pylori isolates were examined in this study, and the isolates were 8073, 8091, and 8099. You might want to remember this particular number here, 8073, because it will occur again. The sponsor has concluded that RBC killing is greater than that of its components.

The in vivo data of RBC versus components, a mouse model was used. One H. pylori isolate was tested, 4187E, and the results that RBC was more effective than the admixture of bismuth and ranitidine.

The in vitro studies of RBC plus antimicrobic. Two-dimensional checkerboard analysis was performed, as Dr. Williamson has described before. One isolate was tested, isolate 8073. Amoxicillin was additive. Clarithromycin was synergistic.

In the time kill studies, only one isolate was tested, 3036E. Amoxicillin was indifferent. Clarithromycin gave synergistic results.

In the flow cytometry experiments, one isolate was tested, 3236E. Amoxicillin was additive. Clarithromycin was synergistic.

So, in these studies you had essentially two isolates. These are the same isolate here and then you have this one. So, two isolates were tested by three different methodologies.

In the in vivo RBC plus antimicrobic arm, a mouse model was used. One H. pylori isolate was tested. That is 4187E. This was the same isolate that was tested in the previous in vivo work with the RBC plus components. Amoxicillin -- that study was not done. The combination with clarithromycin showed a synergistic result.

Does bismuth prevent emergence of resistance? Two isolates were studied, 8073 and 8091. This data has already been presented by Dr. Williamson and questioned by

Dr. Craig, so I will not go over it. But I will say that these numbers that I have here are the same as in the briefing document.

Another study that was presented by Dr. Williamson, which I just received very recently and have not had a chance to make a slide of, but that data where he showed the RBC with resistant clarithromycin isolates and that it was effective, two isolates were studied and he showed you the results for one of those two isolates.

So, I would like to go back again to I feel the most important thing I had to say here, is that in the RBC plus clarithromycin study, there were no patients that had both pre and post-therapy susceptibility results.

Again, I ask the question, are there enough microbiological data in these clinical trials that can be correlated with clinical outcome to support establishing breakpoints for the combination of Tritec and clarithro or Tritec and amoxicillin?

Thank you.

DR. CRAIG: I guess we are to the time for discussion and I guess what we might as well do is put the questions up and start the discussion there. I think that will cover many of Dr. Hopkins' questions that he had for the committee.

So, for both 2558 and 2559, specifically the sponsor is currently seeking the following labeling indications, which were presented earlier, but I will read quickly. "Tritec, when used in combination with amoxicillin or also with clarithromycin, is indicated for the treatment of H. pylori associated duodenal ulcers. This therapy has been shown to increase the overall success of treating duodenal ulcers, as defined by ulcer healing and eradication of H. pylori infection with no ulcer recurrence.

"Tritec, when used in conjunction with amoxicillin, is indicated for the treatment of H. pylori associated duodenal ulcers. This therapy has been shown to increase the overall success of treating duodenal ulcers, as defined by ulcer healing and eradication of H. pylori infection with no ulcer recurrence."

However, the company also presented earlier another statement in which they were focusing primarily on just eradication of the organism.

So, the questions we are specifically asked is, do these clinical trials demonstrate the safety and effectiveness of the combined regimen of ranitidine bismuth citrate 400 milligrams b.i.d. times 4 weeks plus clarithromycin 500 milligrams t.i.d. for the first 2 weeks

in patients with active duodenal ulcers?

If the answer is yes, for which indication should it be labeled? Again, very similar as we has this morning, one being for H. pylori eradication and two then talking about so-called overall success with a variety of definitions, including ulcer healing and no ulcer recurrence; ulcer healing and H. pylori eradication; ulcer healing, H. pylori eradication, and no ulcer recurrence.

And then if no, what additional study data are needed?

So, I think we will address that question first, and I guess I would ask our one remaining consultant whether he would have any comments on it. This is our non-voting consultant.

DR. MEGRAUD: So, my opinion. I think that the eradication rate in association with clarithromycin is in the range of what we saw this morning from most of the trials.

What problem I find with this study is the lack of microbiological data, and I am very worried concerning that. I was wondering if it was because it was not planned in the design or because the strains were lost or whatever reason. Do you have an answer to this question?

DR. CIOCIOLA: The cultures were part of the

protocol design. Now, one point we have to remember, this was a multicentered trial such that what we did, we shipped the culture, the biopsies to a central laboratory to be grown in a double-blinded manner. The problem was that we had a number of problems growing the cultures. We had some mold overgrowth and a number of concerns, and that is why we had such low rates of growth on those biopsies.

DR. MEGRAUD: So, I am glad to know that it was planned because it is a treatment to eradicate the bacteria. So, I think it was absolutely necessary to have a design including culture. I am very sorry to see that the data could not be analyzed.

DR. CRAIG: So, shall we start around then, starting with Dr. Reller?

DR. RELLER: This morning we even rephrased the questions to emphasize the primacy of recognition and demonstration of eradication of H. pylori as a comfortable assurance of preventing the recurrence of disease, which is the long-range plan with these combination therapies.

I start there because it seems to me that whether by design or default or quality control or technical difficulties or whatever that the database as regards H. pylori is so woefully inadequate that although I am willing to accept the safety, I am unwilling to accept

any evidence for sure effectiveness in accord with particularly this last part of the revised statement which is different from what was presented in what we had earlier. This regimen has been shown to eradicate H. pylori infection to reduce duodenal ulcers recurrences. There are no data to support that claim.

I would vote no.

DR. CRAIG: Dr. Bertino?

DR. BERTINO: I think we have seen efficacy data in terms of healing of ulcers, but I would agree with Dr. Reller that we have not seen efficacy data in terms of eradication of organisms. So, I think if we are considering the questions to be healing and eradication, then I would have to vote no also.

DR. CRAIG: I guess I would put a comment in here. At least from what Dr. Hopkins presented up there, the one thing that was statistically different from all these studies was in the term of eradication. Am I right?

DR. HOPKINS: Yes.

DR. CRAIG: And that when it came to ulcer healing, that was the one thing in which there was no difference between RBC and RBC plus clarithromycin, or at least there was a numerical difference but not a statistical difference.

DR. COMER: That is the same thing that we had with omeprazole and omeprazole plus clari, that if you have an effective ulcer-healing agent, then you are not going to get better healing when you add an antibiotic. It is kind of impossible.

DR. CRAIG: Dr. Temple?

DR. TEMPLE: It was probably inadvertent, but they did not use the same phrase as was used in the morning. I do not know whether that was intentional, but for the same database to turn on that phrase does not make any sense. So, maybe one can think of the second sentence as saying eradication of H. pylori has been shown to reduce duodenal ulcer recurrence, which is what the morning's version said. My assumption is the intent was to reproduce that.

DR. CRAIG: Yes. What is says is, "H. pylori eradication is associated with the decreased risk of duodenal ulcer recurrence."

DR. TEMPLE: That was intended I presume to be a general statement, not a statement about the data in here. The data in these trials could presumably go in the labeling elsewhere, but this is the indication section. I am sure the intent was to be identical. It does not make sense to have two different standards for the same kind of

thing.

DR. CRAIG: Dr. Webb.

DR. WEBB: I think we should just take as a priori that we are looking at the same wording that was applied this morning. We may have misparaphrased it in some fashion at this point, but we are looking at the same wording from the morning.

DR. CRAIG: Barth, again I just come back to you. Your interpretation of the data is as you stated?

DR. RELLER: In my mind the answer to number 1 and what I have heard this afternoon, be it owing to the multiplicity of analyses, the confusion, what little data -- I am terribly uncomfortable and I simply vote no.

DR. CRAIG: Okay, thank you.

Mary?

DR. FANNING: I just would like to make a comment. I think we should not focus at this point on detailed indication writing. We had a very thorough discussion this morning.

What would be the most helpful is, as you go through the question, for those who feel there is, information there, whether or not you would choose H. pylori eradication -- and we will deal with the labeling around that -- or an overall success measure that has some

clinical endpoints in a simple way.

DR. CRAIG: Dr. Judson.

DR. JUDSON: Yes, I think that is the issue, Barth. I was trying to sort it out for myself. If we are going to define H. pylori as being a surrogate, then the question becomes if the surrogate data is lacking, but the true clinical endpoint data is present, that is, time to ulcer healing at 4 to 6 weeks and ulcer recurrence rates at 6 months endoscopically verified, and the indication that they are looking for is really for the treatment of acute ulcers, here I think we need help from our gastroenterology colleagues. To me the higher level of clinical proof would be whether an ulcer recurs within 6 months or not. I would like to see the micro data.

Obviously, they cannot have a claim for eradication of H. pylori, an antimicrobial claim, and obviously, they cannot say anything about resistance. But can they get a claim for treatment of ulcers?

DR. CRAIG: You are saying because of the lack of microbiology, they can't have a -- for eradication?

DR. COMER: They have shown that.

DR. CRAIG: They have eradication. They got culture negative, but for the culture positive, what they did not have was the microbiology data there. So, for

eradication theoretically you could still do it. Right?

DR. JUDSON: Yes.

DR. NORDEN: There is also a lack of proof that these patients were H. pylori positive to start with.

DR. CRAIG: No.

DR. COMER: Can I clarify?

DR. NORDEN: You do not have the isolates. I am sorry. You just do not have the isolates?

DR. FISHER: I think the only thing that is missing is the isolates. We have got tests by other methods and we have got Dr. Hopkins' data that spread out stuff that you can look at just across the board very nicely from a distance I think. I think we are getting hung up on the isolates and looking at MICs.

DR. HOPKINS: Let me just make one point. If you go with eradication, again you can look at those rates. What the problem is is we have trouble determining what the true eradication rate is. Clearly in every single analysis, when you look at the microbiologically evaluable population, you get statistical difference between the combination regimens and the control arms, but we have trouble determining what the true eradication rate is because they did not assess eradication in unhealed patients, et cetera.

If you are comfortable with an eradication rate somewhere between 80 and whatever it is, 50 percent, that is the decision you need to make if you are going to with eradication as you have in the previous application.

DR. CRAIG: Dr. Fanning.

DR. FANNING: I think that the data is not dissimilar from what was presented with the previous application. I think that what is dissimilar is the susceptibility data and the whole issue around whether one can decide about resistance with clarithro.

DR. CRAIG: Dr. Dunn.

DR. DUNN: I think the data is different in a couple of ways. One is that nearly half of the people were not Hp positive initially, so that what Dr. Hopkins was trying to say about the eradication rates when we have got eradication rates only in the healed, we have only half of the data.

The other thing to look at is you are looking at eradication as a marker for recurrence. We have the recurrence data, and uniformly, with one exception, the recurrence data, if you look at the overall successes, are not significant. The only one that was significant was the life table analysis. All the others are not. The eradication is are you going to use the marker or are you

going to use the actual data.

DR. CRAIG: Dr. Comer.

DR. CIOCIOLA: Dr. Fisher, can I make one comment please about the sensitivities versus the cultures?

DR. CRAIG: Yes.

DR. CIOCIOLA: My earlier point was that we are missing the clinical isolates from the sensitivities. When we determined the eradication rates, as I said earlier in my presentation, we had three different diagnostic tests that we used: CLO test, histology, and culture. The problem that we had was in getting the clinical isolates to determine the sensitivities, not in determining whether or not the patients were infected by using the culture methods.

DR. WILLIAMSON: In fact, just to add to that, we --

DR. COMER: Can I go?

DR. CRAIG: Dr. Comer has the floor.

DR. COMER: I think that we are getting confused with all this data and different analyses. Actually, if you look at it, in the clarithromycin arm the ulcers were healed and the RBC/clarithromycin eradicated the organism as well as it did in the study this morning. I think that we can easily make the same claim that

treatment of H. pylori infected patients with active duodenal ulcers to eradicate H. pylori is valid in the data that has been proposed.

I think that it is not fair to the sponsor to come and say, well, you should have done eradication in non-healed patients when that is not what the agency told them when they were planning their study, and it is a little bit unfair to tell them to do that now. I agree that that would be nice to know.

The other thing that is important to me is that we have all agreed that eradication is the endpoint. I think that unfortunately in this study there was not a sufficient number of patients that made it to the 6 months to really assess recurrence, but I do not think that that is necessary for our discussion. We can show that they eradicated organism. We have assumed that that will decrease the risk of recurrence, and I think that they can make that claim. I do not think we need the actual recurrence data to approve this drug.

On the other hand, on the amoxicillin I think the data is much weaker.

DR. CRAIG: Could I just ask Dr. Hopkins a question? Specifically on number 80 in your handout, specifically when we looked at ulcer recurrence in those

that were negative versus those that were positive, wasn't there a statistical difference? Wasn't it significant?

DR. HOPKINS: In all analyses, whether they were done foreign or domestic, all these are statistically significant. It is just that there is a difference in quality -- you know, the numbers, 4 percent versus 28 percent, versus 42 percent and 57 percent. So, the surrogate holds. It is just not as strong in the U.S.

DR. CRAIG: Maybe one of the ways to find the difference would be to have European gastroenterologists come to the United States and participate in U.S. studies and we send our gastroenterologists to Europe to do the endoscopy in those studies to see if that could contribute to the difference.

DR. HOPKINS: One of the hypotheses that was mentioned early on was the fact that -- the one difference in the study design is that U.S. studies were placebo controlled, and so the U.S. investigators may actually be looking harder for an ulcer and they are finding it. So, there may be actually a positive control bias in the literature, as well as in the foreign data, Glaxo data, where you do not have a placebo control. I do not think it explains all the difference. I think it may be a component of the difference.

DR. CRAIG: So, in my interpretation of at least what you have been saying is that we have statistical differences in eradication and that the rates, although you are not precisely sure, if you look at the various combinations, it is not much different than what we saw for the drug this morning. Am I right in that?

DR. HOPKINS: Yes.

DR. CRAIG: And that, secondly, we also have data to go along to show that using it as a surrogate marker tends to reduce recurrence.

DR. HOPKINS: The only difference is that the numbers are lower, and so the 95 percent confidence intervals were much wider. So, you are less sure about what that true eradication rate is. I think that is the difference.

DR. COMER: For the true recurrence rate.

DR. HOPKINS: Well, the true eradication rate in the eradication analysis and the true anything. The numbers are lower. The true efficacy.

DR. CRAIG: Dr. Fisher.

DR. FISHER: As a gastroenterologist again -- I am sounding like Dr. Fredd in saying we are trying to get away from the idea of saying something that is going to require an endoscopy within the studies. That is what we

headed to this morning, and I think that is what we should be headed to this afternoon as well.

The other thing. I think there is a lot of that in the literature, based on various things in various of the world, that there are differences in not only occurrences but healing rates with various therapies of duodenal ulcer based on where you may be in the country. So, it may have something else to do with something in the foreign studies.

We have not totally examined the demographics of the foreign studies versus the U.S. studies in detail to be able to see if there are differences there, and it may be what is going on. We know in old ulcer studies that there is a higher placebo rate in the United States of healing with some of the initial ulcer therapies that were done versus Europe, and that may have something to do with it as well, whether it is a different patient outlook or whatever.

Dr. Temple?

DR. TEMPLE: I just want to mention one thing Dr. Dunn said. Everything that the last few people have said strikes me as perfectly true, but there is somewhat more uncertainty about the exact level of eradication because of the somewhat lower healing rates. So, when you

do your worst case, there are more people who did not heal so that means there is a larger body of people whose eradication rate is uncertain. That still does not change the facts of what you said, but it does seem worth acknowledging that.

DR. FISHER: Can I just clarify that? Because I keep going back over the numbers and looking at healing rates at 4 weeks. I am having a hard time finding this major difference between the healing rates from this morning's studies and this afternoon's when we take the Hp positive patients. If you take Hp positive patients that we had in the study this morning and look at their healing rates at 4 weeks after therapy and take Hp positive patients in the studies this afternoon, I do not find the difference in the data, and maybe somebody could show it to me. I agree that the numbers are different and what you are dealing with is smaller, but I have not seen this lower healing rate in this group that we are talking about.

DR. COMER: No. This morning it was like 90 some percent.

DR. FREDD: Yes. You are dealing with between study comparisons, but it is 90 percent or more --

DR. FISHER: Well, yes, 80 versus 90.

DR. FREDD: -- in omeprazole plus clari versus

something like 70 percent with RBC plus clari, as I remember the data.

DR. COMER: Yes, 71.

DR. FREDD: So, there is about a 20 percent delta difference there. I do not know what you make out of it except it is important in terms of how many, in the way this thing was done, as Dr. Temple said, were able to be assessed for eradication.

On the other hand, because a lot of people were unhealed and were not assessed for eradication, if you assume that actually the RBC plus clari is going to have some efficacy to eradicate more than the other arms, it is actually a worst case against them, the fact that they have had fewer patients healed because they have a harder row to hoe.

DR. TEMPLE: Yes. I was not trying to make a big deal out of it. It is just there are more people whose status is uncertain. So, when you do a worst case and assume that everybody who is uncertain did not eradicate, you have a lower worst case, not to make more of that than it is.

DR. COMER: So, I voted yes for everything.

DR. CRAIG: Dr. Judson, did you want to have one other comment?

DR. JUDSON: I was just going to make a passing philosophic comment. Dr. Roy Anderson of the U.K. quoted a colleague sage of his once who said something to the effect that there is no problem in the world, no matter how complicated and how confusing, when looked at in just the right way, cannot be made to seem more complicated and more confusing.

(Laughter.)

DR. JUDSON: Somehow I think we have been doing that.

DR. CRAIG: Well, Barth, you are still where you are. Right? Move on to the next or are you reconsidering a statement?

DR. RELLER: I liked the comment that was made. They are 70 percent and 90 percent. The numbers are much lower in the 70 percent, and there gets a point at which the numbers are so low that you are very uncomfortable, and I am still very uncomfortable.

DR. CRAIG: Dr. Bertino?

DR. BERTINO: I think, based on the discussions just now, I would vote yes.

DR. CRAIG: Dr. Norden.

DR. NORDEN: I am glad we had these discussions before I had to vote.

I would vote yes with exactly the same labeling basically as we did this morning.

Just to speed up and save time, in terms of what additional studies are needed, it is clear to me that the company needs to do some very basic microbiology studies, and I do not think there is data to support any comments about resistance in the information that they have submitted.

DR. CRAIG: Dr. Kirschner?

DR. KIRSCHNER: I think the results for the results at 4 weeks and 24 weeks were similar enough to what we had this morning that I vote yes.

DR. CRAIG: Dr. Fisher?

DR. FISHER: I have actually got two proxy votes here. Dr. Elashoff is voting yes, except she actually prefers the indication that was initially put forward by the sponsor. Her quote here is, "I prefer this indication to the newer one they presented, since there is little in their data to suggest reduction of ulcer recurrence." I think she was going to the old one you put up, though, as opposed to the exact one this afternoon, and she did want specific reference to Hp eradication to be made.

Dr. Banks-Bright said no. Poor microbiological

data.

And I am saying yes with the new wording that we had that was as this morning's.

DR. CRAIG: I am also saying yes with this morning's wording.

We have already Dr. Comer.

DR. COMER: Yes.

DR. FISHER: Dr. Dunn.

DR. DUNN: No, because the sample sizes are very small and the actual data, as opposed to the surrogate data, say there is not a difference.

DR. FISHER: Dr. Butt.

DR. BUTT: Could I ask Art a question first?

DR. FISHER: Surely.

DR. BUTT: Is the problem that you isolated organisms, but when you tried to do the subcultures to get the sensitivities, you fouled them up?

(Laughter.)

DR. BUTT: To put a nice edge on it.

DR. CIOCIOLA: Yes, thank you.

Maybe Dr. Weissfeld, who is the Director at MSI who is the group that did the culture work, could address that.

DR. WEISSFELD: Alice Weissfeld, Microbiology

Specialists.

One of the problems here was -- I think some of you may remember when I talked in October. We learned a lot about the transportation of these cultures, and one of the things that happened here is while we were able to isolate three or four colonies on a plate, there was not enough to do subsequent susceptibility testing because of problems with the way that these were transported on dry ice and skim milk. We had a particularly horrible winter. There were days, up to four or five days, that FedEx could not deliver the packages, so the things thawed and we could not grow very much. We grew some but not enough to do the susceptibility testing.

DR. BUTT: But there was a primary isolation.

DR. WEISSFELD: There was a primary isolation, but the number of isolates that we were able to do susceptibilities on was only 25 percent of the total number of isolates that we actually grew out.

DR. BUTT: Okay, if it is 25 percent, why did we only have sensitivity data on two organisms, the two identified isolates?

DR. WEISSFELD: Well, what happened was there were some cases where -- I think what they were trying to show you were paired specimens. There are more

susceptibility data than there are first and second or first and third or first and fourth visits. So, there were not very many people who had paired results because of the fact that the pre-study susceptibilities hid at the time where we had the problems in getting enough growth to be able to actually perform the susceptibility tests.

DR. BUTT: So, the statement that there was no resistance encountered is a gross overstatement. Is that right?

DR. WEISSFELD: There was resistance encountered but not in the arms that you were looking at. The resistance that was encountered when the blind was broken turned out not to be in the one with combination treatment.

DR. CRAIG: It looked like you had more of your data in the post-cultures. Those were the ones post therapy.

DR. WEISSFELD: That is correct.

DR. CRAIG: It was in the pre-therapy that you lost most of your specimens.

DR. WEISSFELD: That is correct. Exactly.

DR. JUDSON: Why is it if you had even one colony, you could not go back and grow them out again and start over?

DR. WEISSFELD: This organism is extremely fastidious, and it does very poorly on subculture. We have since then worked out much better systems for subculturing the isolates.

The other problem was when this was originally set up, the sponsor told us to batch the susceptibilities, and so the ones that were frozen away were actually retrieved en masse, so to speak, at specific intervals from the freezer, and that was a very poor decision also.

What we do now is, as soon as a culture grows, we set up the susceptibilities again because the organisms do not do very well coming out of the freezer. Usually when you do a susceptibility test from an organism from the freezer, you have to pass it three times in order to get it to do correctly in the susceptibility test, and that was not even possible in these studies.

So, I think that part of this was a learning process as far as doing the susceptibility test and part of it was the fact that we were not starting out with a good number of organisms. There is no enrichment broth is what I am trying to tell you like there is for some of the organisms that you are familiar with to get up the numbers like you need to do the subsequent susceptibility testing.

I heard somebody say that the sponsor should

collect microbiological data. The situation is going to be a lot different for the sponsor now if they try to do that with what we learned during the study, but the fact is that the culture isolates were actually grown. It was just the susceptibility data that was a problem.

DR. BUTT: Well, I guess I will vote yes, but I think we need the microbiologic susceptibility data and there is a serious weakness in the presentation because we do not have that.

DR. CRAIG: Dr. Judson.

DR. JUDSON: Yes, with the same caveats.

DR. CRAIG: Dr. Rice.

DR. RICE: I guess I am the last voter today.

I have raised some of the same concerns that Dr. Reller had raised. I am very uncomfortable. I am on the verge of abstaining or voting no more around the question -- I guess I pose it back to the laboratory or Dr. Williamson -- if you have concerns or problems with recovering for susceptibility testing, are we assured that we do not have false negatives in this eradication arm?

DR. HOPKINS: The criteria for defining eradication was set forth by the Division of Anti-infective Drug Products and is used by all sponsors whether that is correct or not. But essentially you do not need culture to

define eradication in our criteria. It is helpful and we recommend it to assist us with the diagnosis of eradication and infection, but you do not need it. You only need two tests and those two tests can be histology and CLO. So, it is still fairly stringent the way they defined eradication even if they did not culture.

DR. WEISSFELD: I think that is the answer to the question. I cannot do any better than that.

DR. RICE: I will still have to abstain.

DR. CRAIG: The final vote that I have then is 9 yes, 3 no, and 1 abstain.

Should we do the next one then with amoxicillin, or do we want to do the second question here? Do the clinical studies or supporting data demonstrate that each component of the regimen contribute to the claimed efficacy? We are talking only about eradication here since we, in essence --

DR. COMER: I think we answered that, didn't we?

DR. CRAIG: Do you want this question answered? I will say yes if you do.

(Laughter.)

DR. FANNING: We would like it answered if you feel that you have enough information to do that.

DR. CRAIG: At least my wording of it is we are looking at it from what we said before and making it similar to this morning where we are talking specifically about eradication. I would say from the data that was presented, the answer is yes.

DR. HOPKINS: This is really a regulatory question, and one of the problems is that the data that was actually presented by the sponsor has not been fully reviewed by the agency. It was just recently submitted within the last month. The literature review is something we will look at, but we have not really had the opportunity to really critically look at that data.

DR. CRAIG: But you are looking at further -- I guess what I was looking at was whether RBC versus RBC plus clarithromycin --

DR. HOPKINS: We do not need to ask that question.

DR. CRAIG: Okay. You are quite happy about that.

But the one that you are trying to get us to ask is whether you are talking about ranitidine plus bismuth.

DR. HOPKINS: Yes.

DR. CRAIG: I do not think we can answer that.

DR. FISHER: No. Can I make a suggestion? What we have done sometimes in the past on the GI Committee when something like this has come up is that we take a vote to recommend to leave it up to the agency to work it out with the sponsor, and if there are concerns on the part of the agency, that they bring it back to the committee or to the joint committee for further information.

There is a second on that motion?

DR. CRAIG: Yes, because we have been only presented data from the literature, nothing from any trials. Does everyone agree with that?

DR. COMER: Yes.

DR. CRAIG: Okay. So, could we go on to the next one then which essentially is the same thing except now amoxicillin is substituted for clarithromycin? So, we will start around the other end this time. Dr. Rice? I guess I should give our consultant a shot first.

DR. MEGRAUD: I really think that the data including amoxicillin are too weak to support this indication.

DR. CRAIG: Dr. Rice.

DR. RICE: Thank you. Again, I have the same concerns. I abstain.

DR. CRAIG: Dr. Judson.

DR. JUDSON: I also think the data is just simply too weak and would vote no.

One of the things that concerned me, though, is that when we are talking about the additional efficacy that is accomplished by adding, say, clarithromycin to Tritec versus clarithromycin to omeprazole where we saw no difference, at least in terms of healing at 4 to 6 weeks, how much of that is simply due to the fact that Tritec, namely, ranitidine, is not as effective as omeprazole? So, you would also be able to get an additive effect or a synergistic effect if your standard, your strom N, is a weaker one.

I worry that methodologically that can be a problem with other studies where what you start with is not as good a cure for ulcers in itself.

DR. CRAIG: Dr. Butt? Oh, wait. A question here for Dr. Temple.

DR. TEMPLE: Well, that would be possible, but in fact neither one showed a contribution to healing rate even though they had a better shot at it in this one.

DR. JUDSON: Yes, that is all I am saying. Looking at their graphs, even though these things were not statistically significant, they could give a strong graphical impression that each one was additive.

DR. CRAIG: Dr. Fredd.

DR. FREDD: You say this data is weak. What data are you referring to? Do you mean that the eradication data is too uncertain or the number that they have gotten is too low for approval?

DR. JUDSON: I am sorry. I think the overall activity and efficacy of amoxicillin is too weak.

DR. CRAIG: Dr. Norden.

DR. NORDEN: Before we go around and vote on this, because I would completely agree with the vote no to the proposed label, but the question is would one want to substitute for the labeling that to use this in patients who are known failures with clarithromycin or where sensitivity testing has been done and the organism is clarithromycin-resistant because I would certainly vote no also for what we have at present. But clinically we have in a sense no alternative where there is data. This is the only data that I know of from a controlled trial.

DR. CRAIG: Dr. Webb?

DR. WEBB: The initial labeling we did put in our proposal was exactly like that essentially, that it was in patients who are known to have resistance to macrolides or cannot tolerate macrolides. The amoxicillin regimen is a backup alternative regimen, and I think it would be

better personally for clinicians to have more than one alternative when it comes to this.

DR. CRAIG: Dr. Utrup?

DR. UTRUP: I think it would be essentially impossible to ascertain resistance with clarithromycin and Tritec because we have no data to evaluate what the breakpoints might be. So, I do not know how you could put that in a label. We saw that there was a difference between omeprazole and clarithromycin, so are we sure that there is not a difference between Tritec with clarithromycin?

DR. CRAIG: Dr. Butt? Oh, we have a question. Dr. Bertino?

DR. BERTINO: For Dr. Hopkins, the question is safety and effectiveness of this regimen with amoxicillin. Based on your analysis -- I am looking on page 51 of your handout -- is RBC plus amoxicillin more effective in treatment of duodenal ulcers or is it at least as effective as RBC alone? Is that what these graphs say?

DR. HOPKINS: Are you looking at page 49 where I represent the eradication data in the microbiologically evaluable population?

DR. BERTINO: 51.

DR. FISHER: Page 51.

DR. HOPKINS: Well, this is ulcer healing.

DR. FISHER: Right. That is what he is asking.

DR. HOPKINS: No, there was no statistical significance between 73 percent and 66 percent, nor was there statistical significance between 77 percent and 70 percent in the observed healing analysis. There was no statistical difference between the combination RBC and amoxicillin and RBC alone. Dr. Kay Dunn can confirm that in ulcer healing.

Why ask the question?

DR. BERTINO: The question up here says, "Do these trials demonstrate safety and effectiveness." So, safety aside -- we have heard the safety data -- RBC plus amoxicillin was effective. It was as effective as RBC alone. See, I do not know what we are comparing it to in this question.

DR. FISHER: I think we are going for the same thing on eradication. That is what we have come to.

DR. HOPKINS: Integral into the question is defining what efficacy parameter you want to use to label. If you are going to use eradication, then you should use eradication. If you are going to use something else, then state that.

I gave two options of eradication and overall

success. If you want to use healing, I suppose you could put that on the list. But you need to define what your indication is at the same time as deciding how efficacious it is.

DR. CRAIG: And also each of the components need to contribute to that.

DR. HOPKINS: Right.

DR. CRAIG: Which, in essence, if we looked at healing where we see equal healing with RBC, we do not have any evidence that the clarithromycin is contributing to that.

DR. HOPKINS: Right. There is no evidence that the antibiotics contribute to healing. If you were going to go with healing, you would --

DR. COMER: That is why we did not go --

DR. CRAIG: I agree. I was just trying to reiterate that point.

Any further comments before we continue the vote? Yes, Dr. Reller.

DR. RELLER: I just wanted to raise a question. Given the hour and given the complexity of the data, I wonder whether it is worth a detailed discussion on one more point or one point or whether it might be more helpful to the agency to have a show of hands, yes or no, because

there is a whole other page of questions here that I think may be pretty straightforward.

In other words, is the sense of the committee conveyed to the agency of more use than a detailed discussion and never getting to the other questions? I just raise the question.

DR. COMER: Please let us vote.

DR. CRAIG: Do you want to vote by a show of hands?

DR. RELLER: Let's just zip through them and vote by a show of hands.

DR. CRAIG: Let's go on the question of still should it be yes for this question. So, all those in favor of a yes, raise their hands.

DR. FISHER: I have to vote for Dr. Elashoff, who voted yes.

DR. CRAIG: All of those that are voting no, raise their hands.

(A show of hands.)

DR. CRAIG: And we have one abstention.

DR. FISHER: Can I actually throw in another question for a vote which may help the agency?

Oh, Dr. Banks-Bright voted no.

Could I ask if the question could be raised to

give an indication for this as second line therapy in patients who are intolerant of macrolides, or does the group not want to discuss that? Dr. Judson?

DR. JUDSON: Intolerant and/or have failed.

DR. COMER: I would like to add a clinical aspect to this. Basically I think that 40 percent eradication is inadequate and I would treat a patient intolerant to macrolides with amoxicillin and flagyl. Regardless of whether we have a labeling or not, I think that that is what a lot of clinicians would do. I do not think that it is prudent to advocate a treatment that is not good enough to warrant a single antibiotic regimen. I think we would treat with two drugs. We would add flagyl to the amoxicillin in this kind of patient.

DR. FISHER: I withdraw my question.

DR. CRAIG: I guess we can then go on to the questions that apply to both Glaxo applications. Will someone put up an overhead on those?

The first one. Is it appropriate to broaden the indication to patients with a history of duodenal ulcer disease but without an active duodenal ulcer? All those that are in favor of yes to this answer, raise their hands.

(No response.)

DR. CRAIG: All those that vote no, raise your

hand.

(A show of hands.)

DR. CRAIG: Yes.

DR. TEMPLE: Can I ask you what you think the indication that you agreed on for both drugs means? I read it as people with active duodenal ulcer disease, but I did not read it as necessarily having to have an ulcer at the moment you start. Is that how you all read it?

DR. COMER: No.

DR. TEMPLE: So, active duodenal ulcer means people with a good active history, even if they do or do not have an ulcer at this very moment.

DR. FISHER: I did not take it as that. I took it was what the studies were presented as, in patients who have an active duodenal ulcer.

DR. TEMPLE: Then I want to raise the question I raised this morning again. I by mistake healed somebody's ulcer without an antimicrobial regimen. Is it my obligation to wait till he recurs again, or do you really think I should treat him?

DR. CRAIG: I guess my question is I would like to see data simply from the fact that I could understand how the absence of inflammation might affect the penetration of the drug, the ability to get to the mucus,

but I can also look at it from the other side that with the absence of an ulcer, you may be dealing with a smaller number of organisms and it may be even easier resulting in a better result in that situation. But I do not think we can state until we specifically see data.

DR. TEMPLE: You think it is reasonably likely that you need an ulcer in order to succeed in eradicating.

DR. CRAIG: No. I think that the rates may vary depending on whether there is an ulcer or whether there is not an ulcer. Then you start maybe getting down to the rates where, if it is less, what we did with amoxicillin where we decided that it was not a high enough rate.

DR. COMER: It is not going to stop anybody from treating them, Dr. Temple.

DR. TEMPLE: I know. We do not like the labeling to be --

DR. COMER: You do this all the time to us.

(Laughter.)

DR. COMER: You want us to make decisions based on data that is not there, and yet the agency is telling us that we have to go on the data that is presented and not extrapolate when the data has not been presented. I think that that holds and I think that we are going to continue

to vote like that and that it is not fair of you to push us otherwise.

DR. TEMPLE: First of all, I am just asking because we do need to know.

And second of all, one of the reasons you come to an advisory committee is to get judgments, and the judgment can go in some cases beyond the data depending on what you think. For example, if you had a person who was on maintenance for duodenal ulcer disease, does that person have active duodenal ulcer or doesn't that person?

I just find it a little odd that you have to wait for them to recur, and in fact, in a person who is on maintenance, there is sort of no way to get out of this, is there? You have to keep them on it forever.

DR. COMER: Dr. Temple, what you do in your clinical office is different than what we want to decide and whitewash in this committee. We are not telling people how to practice medicine and if I had a patient who had an ulcer and was Hp positive and he did not get treated, I would probably treat them. But that is not relevant to the discussion that we are having today, and you keep doing this. You keep trying to put clinical scenarios --

DR. CRAIG: Well, we have voted no. We have voted no, so we have already done it. So, let's move on.

Dr. Fredd, real quick.

DR. FREDD: Just one slight thing and that is you are not saying de novo acute ulcers. You are saying acute ulcers in patients who may have a history of ulcer disease for many, many years, but they just show up with an acute ulcer. Is that correct?

DR. CRAIG: Yes.

DR. FREDD: They have an active ulcer but it is not the first presentation of the active ulcer because in this database, these people have had ulcer diathesis for years.

DR. CRAIG: Sure, we agree.

DR. FISHER: I also agree that we have not said that you have to have an acute duodenal ulcer proven by endoscopy, and people treat people for acute duodenal ulcer with an old history on the basis of symptoms and the diathesis.

DR. CRAIG: The second question is, are there enough microbiological data in these clinical trials that can be correlated to clinical outcome to support establishing breakpoints for the combination of Tritec and, A, clarithromycin?

We will take a vote there. We will start with no first. All those in favor of no, raise their hands.

(A show of hands.)

DR. BERTINO: Dr. Reller.

DR. CRAIG: And I have also two others here, and I think that is everybody. So, yes, just to be sure?

(No response.)

DR. CRAIG: There are no votes for yes.

For amoxicillin, we will do it the same way. No, raise your hands.

(A show of hands.)

DR. CRAIG: Yes?

(No response.)

DR. CRAIG: Nobody.

The potential for resistance among H. pylori strains to clarithromycin is likely related to patient compliance (often related to side effects) and the number of patients who fail therapy.

I think, if anything, the data suggested that -- oh, wait.

DR. FISHER: Read the next part.

DR. CRAIG: I take it back.

Is there sufficient information from the clinical trials to suggest that the market approval of Tritec in combination with clarithromycin will lead to increased clarithromycin resistance among H. pylori

isolates?

All those in favor of an answer of yes to that, raise your hand.

(No response.)

DR. CRAIG: All those that answer no, raise your hands.

(A show of hands.)

DR. CRAIG: So, everybody was unanimous for no for all three of those questions.

Are there any other questions that are needed, Dr. Fanning?

DR. FANNING: No.

I would like to thank the committees for sliding through some very difficult data and giving us --

DR. CRAIG: I might also just add for the record there were no requests for the open public hearing, and so, therefore, we can adjourn this meeting.

Thank you.

(Whereupon, at 5:05 p.m., the committee was adjourned.)